DEPARTMENT OF CHEMISTRY AND BIOLOGY

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

Ph.D. Thesis in Chemistry

Asymmetric synthesis of Heterocyclic Compounds through cascade Carbon-Carbon and Carbon-Heteroatom bond forming processes.

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List of abbreviations

AIBN	2,2'-azobis (2-methylpropionitrile)
Alk	alkyl
Bn	benzyl
Boc	tert-butyl carbamate
br	broad
Bu	butyl
C	concentration
Cbz	benzylcarbamate
cat.	catalyst(s)
d	doublet
DCM	dichloromethane
dd	double doublet
DEPC	diethylphosphoryl cyanide
DIBAL-H	Diisobutylaluminium hydride
DKR	Dynamic Kinetic Resolution
DMAP	4-(Dimethylamino) pyridine
DMF	dimethylformamide
DMM	dymethylmalonate
DMSO	dimethylsulfoxide
DNA	DeoxyriboNucleic Acid
dr	diastereoisomeric ratio
EDC	3-Dimethylamino-propyl-ethyl-carbodiimide
EDG	Electron Donating Group
EWG	Electron Withdrawing Group
EI	Electron Impact
ee	enantiomeric excess
er	enantiomeric ratio
equiv.	equivalent(s)
ESI	electrospray ionization
Et	ethyl
EWG	Electron Withdrawing Group
H	hydrogen

h	hour(s)
HOBt	Hydroxybenzotriazole
HPLC	high performance liquid chromatography
HR-MS	high resolution mass spectrometry
Hz	Hertz
i	iso
IR	infrared spectroscopy
m	*meta*
m	multiplet
M	molar (concentration)
MALDI	Matrix-assisted laser desorption/ionization
Me	methyl
min	minutes
m.p.	melting point
MS	molecular sieves
MTBE	methyl *tert*-butyl ether
m/z	atomic mass units per charge
NBS	*N*-bromosuccinimide
NMO	N-Methylmorpholine N-oxide
NMR	nuclear magnetic resonance spectroscopy
NPs	2-Naphtyl sulfonyl
Nu	nucleophile
o	*ortho*
OC	organocatalysis
p	*para*
PG	protecting group
Ph	phenyl
Pr	propyl
PTC	Phase Transfer Catalyst/ or catalysis
q	quartet
rac	racemic
RNA	RiboNucleic Acid
r.t.	room temperature

s	singlet
t	*tert*
t	triplet
T	Temperature
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
Ts	Tosyl group

1. Introduction

1.1 Heterocycles

The aim of this PhD thesis is the synthesis of new heterocyclic compounds of pharmaceutical interest through the development of new carbon-carbon and carbon-heteroatom bond forming reactions.

As known, some of the most important molecules in nature contains heterocycles. The most common heterocycles are those having five or six membered rings and containing heteroatoms as nitrogen (N), oxygen (O), or sulfur (S)[1].

Given their ubiquitous presence in nature, they play an essential role in many fields of organic chemistry.

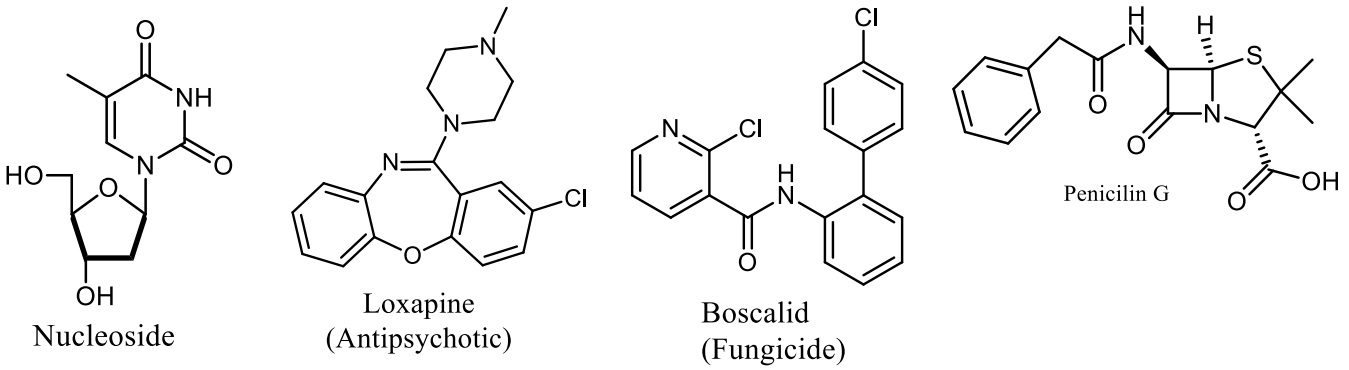


Figure 1.1.1

Heterocyclic chemistry constitutes about sixty-five percent of organic chemistry literature[2] and they have a wide range of applications: they are predominant as pharmaceutical[3] compounds and they find applications in sanitizers, developers, antioxidants and as starting materials in the synthesis of other organic compounds.

A large number of natural products have a heterocyclic moieties as penicillin cephalosporin, alkaloids such as reserpine, morphine, vinblastine. This is one of the reasons because they are very relevant in organic synthesis and in medicinal chemistry: some parts of their moieties can be manipulated to achieve significant modification in function. Modifications can be fitted with other groups that have some similarities in their proprieties. Modifications can include polarity[4], basicity, acidity or the change of one heteroatom for another ring and different positioning of the same heteroatoms in other positions.

The history of heterocyclic chemistry began in 1800[s] in step with the development of organic chemistry. In 1818 Brugnatelli isolated alloxan from uric acid, in 1834 he obtained pyrrole from dry distillation of bones,

[1] E. Vitaku, D.T. Smith, and J. T. Njardarson, *Med. Chem*. **2014**, 57, 24, 10257–10274
[2] R. Gupta, M. Kumar; *Heterocyclic Chemistry*, **1996**, 1, 98
[3] A. Czarnik; *Acc.Chem.Res*, **1996**, 29, 112
[4] T.L. Gilchrist, *Heterocyclic Chemistry*,**1992**,3,1.

and in 1936 Treibs isolated chlorophyll derivatives from crude oil to explain the biological origin of petroleum.

To understand better the importance and the versatility of the heterocycles in organic chemistry, we need to look at the mimicking power they have. Several heterocyclic compounds can be used to provide other functional groups. For example, tetrazole ring is a good alternative[5] to the carboxylic acid because of its acidity and steric requirements. Tetrazole group presents metabolic stability and bioavailability. Furthermore, the nitrogen atoms in the ring can create a great charge distribution.

Once clarified the importance of heterocyclic compounds in organic synthesis and understood the importance of their biological proprieties in life, we need to point out that the activity of this kind of molecules can change according to stereochemistry of existing stereogenic centers.

From a structural point of view, heterocycles can be divided in aromatic and non-aromatic that can host one or more stereogenic centers in the scaffold. Several studies demonstrated that biological activity is strictly related to the stereochemistry of molecules. About that the need to find many new synthetic strategies to reach out this kind of enantioenriched molecules is of paramount importance not only for synthetic organic chemistry but also for medicinal and industrial chemistry.

1.2 Non-aromatic heterocycles

Several classes of molecules with relevant biological activity, contain non-aromatic heterocyclic structure in their scaffolds. Most of them can be found in many natural and synthetic products, for example Isoindolinones, Phtalides and Isoquinolones, showing interesting and diversified biological activities.

Our interest focused principally on these 3 classes of compounds also because they are structurally connected to each other. Isoindolinones and phthalides are isosters, while isoquinolones are superior homologues of isoindolinones.

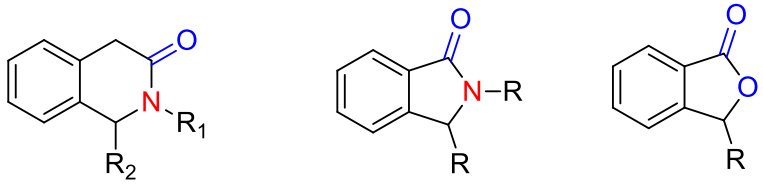


Figure 1.2.1

[5] W.O.Foye,L.Thomas; Foye, *Principles of medicinal chemistry*, **2007**,6,754.

For example, the 3- or 3,3-disubstituted isoindolinone motif is a frequently encountered in numerous bioactive natural products and a large family of pharmaceutically active compounds[6] with anticancer activity, serotonin modulators receptors, HIV-reverse transcriptase inhibitors and so on.

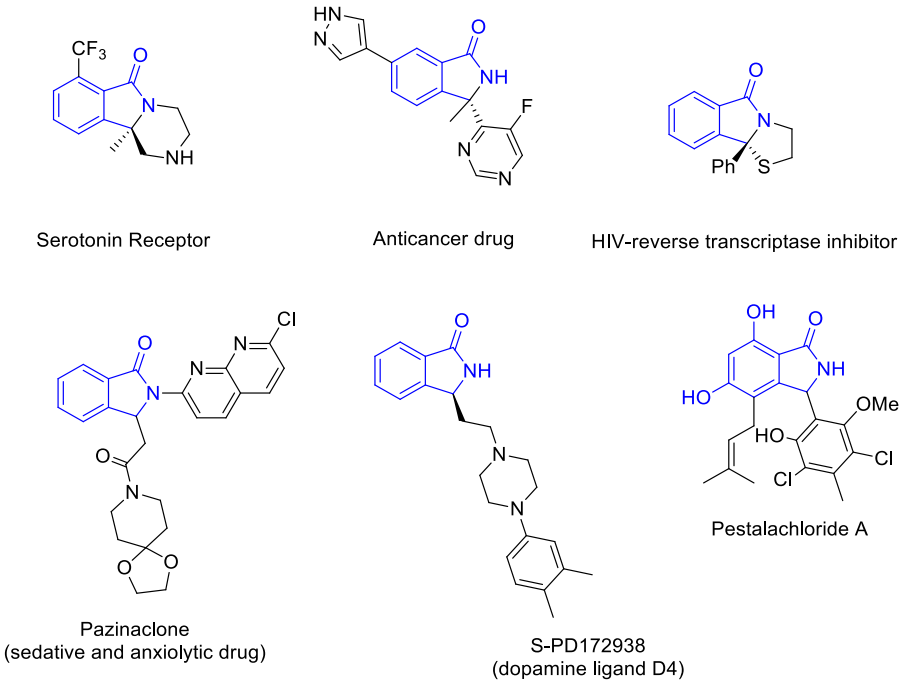


Figure 1.2.3

Phthalides and their corresponding dihydro, tetrahydro, and dimer analogues are found as constituents of several genera within family of Apiaceae. For instance, Ligusticum and Lomatium species are used among certain Hispanic and Native American cultures being employed for a multitude of illness as pneumonia, colds, viral infections as tuberculosis[7].

[6] K. Speck, T. Magauer, *Beilstein J. Org. Chem.* **2013**, *9*, 2048–2078

[7] Bye, R. A.; Linares, E.; Botanico, J. *J. Ethnobiol.* **1986**, *6*, 289-306

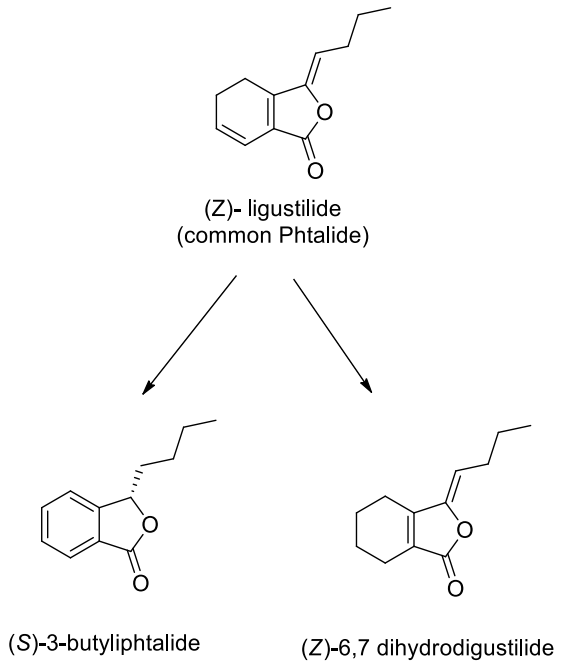


Figure 1.2.4

According to literature, the majority of beneficial effects of these kinds of compounds is strictly linked to the natural precursor, (Z)- Ligustilide. Currently over 40 derivatives of Ligustilide, are known, synthetic and natural ones, and time after time, several studies demonstrate activity of different type of Phthalides in many therapeutic fields: anticholinergic[8] activity, asthma, ischemic stroke, antihypertensive modulator[9].

Over fifteen isoquinolone alkaloids are presently known. They can be found in aromatic form or even partially reduced form.

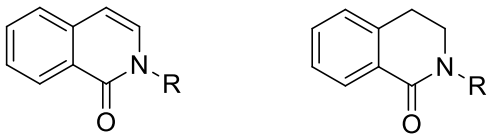


Figure 1.2.5

Isoquinolones may originate in nature from the oxidation of benzylisoquinolines. It is possible, however, that they may also be formed from the in vivo oxidation of protoberberines, phthalideisoquinolines, or even spirobenzylisoquinolines[10].

This class of compounds is under current investigation in oncology drug research, because recent studies identify isoquinolones as potential modulator of many proteins in cell cancer growth.

[8] Mitsuhashi, H.; Nagai, U.; Muramatsu, T.; Tashiro, H. *Chem. Pharm.Bull.* **1960**, *8*, 243-245.

[9] Ko, W.-C.; Chang, L.-D.; Wang, G.-Y. *Phytother. Res.* **1994**, *8*, 321-326.

[10] *Journal of Natural Products* **Vol. 45,** No.**4**

In particular, some derivatives may engage aromatic π–π stacking interaction and van der Waals contacts in the p53 binding pocket of MDM2 acting as potential inhibitors[11].

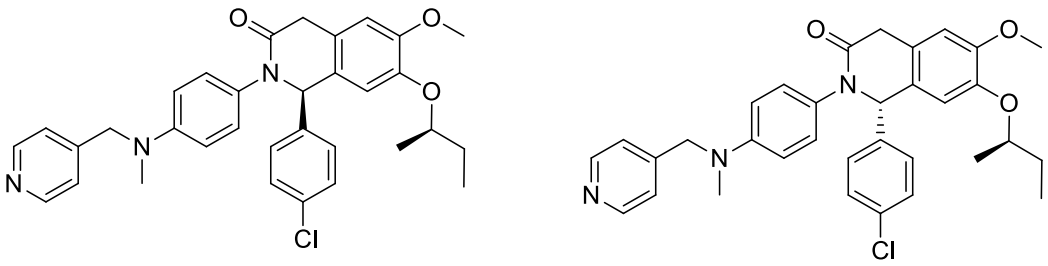


Figure 1.2.6

According to previous examples, it is clear that the synthesis of these structurally related classes of compounds represents a new frontier and challenge in organic synthetic methodologies for the role they play in numerous fields of chemistry. But it is also evident that their activity cannot be untied from chirality of heterocyclic scaffold. As we have seen, structure of these class of compounds isn't totally flat. They are mostly composed by aromatic ring fused with a 5-6 membered ring that can contain a stereocenter meaningful for biological activity of compound. It means that different chiral topology of compounds can influence binding with receptor or enzyme, therefore, different pharmacological effects. However, the number of asymmetric methodologies in the synthesis of these classes of chiral compounds are limited.

Therefore, it's obvious, synthesis of heterocyclic compounds cannot be stopped to synthesis of scaffold, but also, we need to look a certain type of synthesis who can assure a certain control of the stereochemistry of final product.

To this purpose, organocatalysis could be an effective strategy in order to face the double challenge represented by asymmetric synthesis of these classes of compounds.

1.3 Chirality and importance of asymmetric synthesis

As known, the methodologies to get enantiopure compounds are mainly three:

Racemic resolution: this kind of process involves conversion of the racemic mixture to a pair of diastereomeric derivatives by reacting them with chiral derivativeizing agents, also known as chiral resolving agents. Diasteroisomers present different chemical proprieties, so they can be easily separated to reach out the pure enantiomer through removal of the chiral derivativeizing agent.

[11] *Bioorganic & Medicinal Chemistry Letters*, 2015, 25(17), 3621-3625

This type of resolution is usually employed in pharmaceutical industries because particular reaction conditions are not required, even though several operations are required and the final yield is only ideally 50% with the waste of the undesired enantiomer.

Chiral pool: is a strategy that employs available enantiopure building blocks, as amino acids, sugar or terpenes, in total synthesis to achieve enantiopure products.

Asymmetric catalysis: divided in biocatalysis and chemocatalysis. It is particularly appealing thanks to the use of a catalyst in low amount, which in principle can be recovered and reused.

Biocatalysis: this kind of approach is based on the use of enzyme or biological compounds to achieve chemicals transformations. This strategy was found very useful to achieve very high ee in the final target compound using very mild conditions.

Chemical catalysis: divided into metal complexes catalysis, which are typically chiral coordination complexes with transition metals, and organocatalysis.

Organocatalysis consists of using of small organic molecules as catalysts, containing in the structure carbon, nitrogen, oxygen or sulphur group enable to establish selective interaction with the substrate to get enantioenriched compound[12].

In the past decade, organocatalysis has proven to be an attractive tool for synthesis of enantiomerically enriched compound. It is recognized as an independent synthetic toolbox besides asymmetric metallic catalysis end enzymatic catalysis of chiral organic molecules, because it has shown multiple advantages compared with the other two catalytic areas previously cited. In general, organocatalysts are non-toxic and robust compounds. They are commercially available or can be easily synthetized. This class of catalysts doesn't require inert reaction conditions because they are usually stable under aerobic conditions and are able to perform reactions under mild conditions and high concentration avoiding a large amount of solvent and minimizing the waste[13].

Organocatalysts may act through two different pathways: they can activate the nucleophile or electrophile (or both of them in the case of bifunctional catalysts), and they can create an asymmetric environment for setting the chirality of final product.

Generally, the organocatalysis can be divided in two classes, according to their interactions with the substrate: covalent or non-covalent catalysis:

[12] K. A. Ahrendt, C. J. Borths and D. W. C. MacMillan, *J. Am. Chem. Soc*., **2000**, 122, 4243–4244.

[13] J. Aleman and S. Cabrera, *Chem. Soc. Rev*.**, 2013**, 42, 774-793.

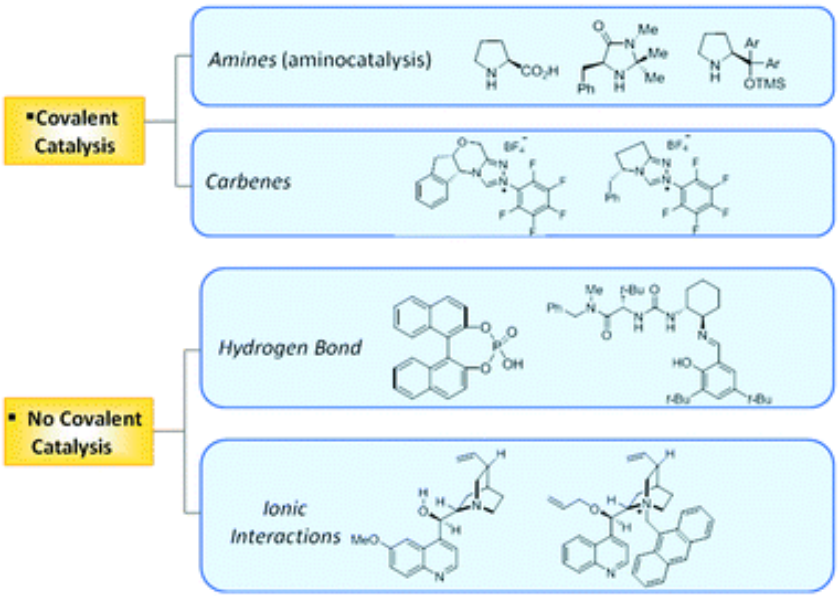


Figure 1.3.1

In covalent catalysis, we have a covalent bond between the catalyst (aminocatalyst[14-15], or carbenes[16]) and the substrate, in order to increase interaction with the reagent in the reaction mixture.

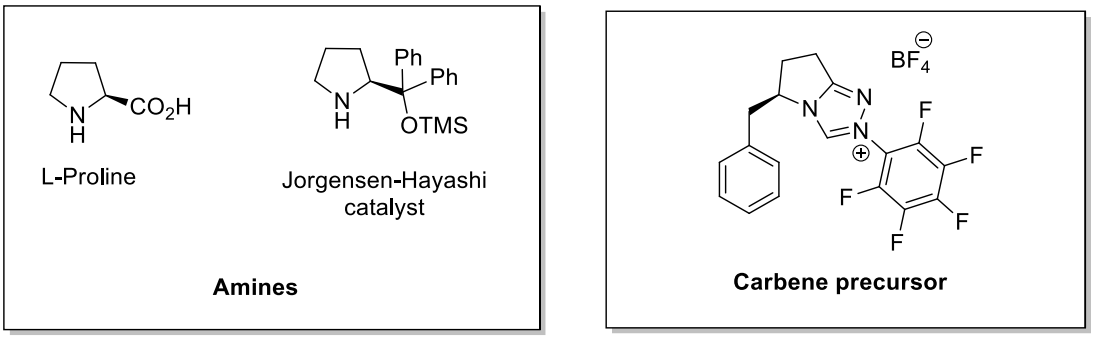


Figure 1.3.2

In the case of non-covalent catalysis, the activation of the substrate occurs mainly *via* hydrogen bond[17] (thioureas, squaramides and phosphoric acids) or ionic interaction (Phase Transfer catalyst)[18].

[14] B. List, R. A. Lerner and C. F. Barbas, *J. Am. Chem. Soc.* **2000**, 122, 10, 2395–2396.

[15] J. Franzén, M. Marigo, D. Fielenbach, T. C. Wabnitz, A. Kjærsgaard and K. A. Jørgensen, *J. Am. Chem. Soc*, **2005**, 127, 18296– 18304.

[16] A. Grossmann and D. Enders, *Angew. Chem*., Int. Ed., **2012**, 51, 314–325.

[17] P. M. Pihko, *Hydrogen Bonding in Organic Synthesis*,Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, **2009.**

[18]J. Otevrel, M. Waser, Asymmetric Phase-Transfer Catalysis—From Classical Applications to New Concepts, Wiley-VCH GmbH: Weinheim, Germany, **2023**, vol. 2, pp. 71-120.

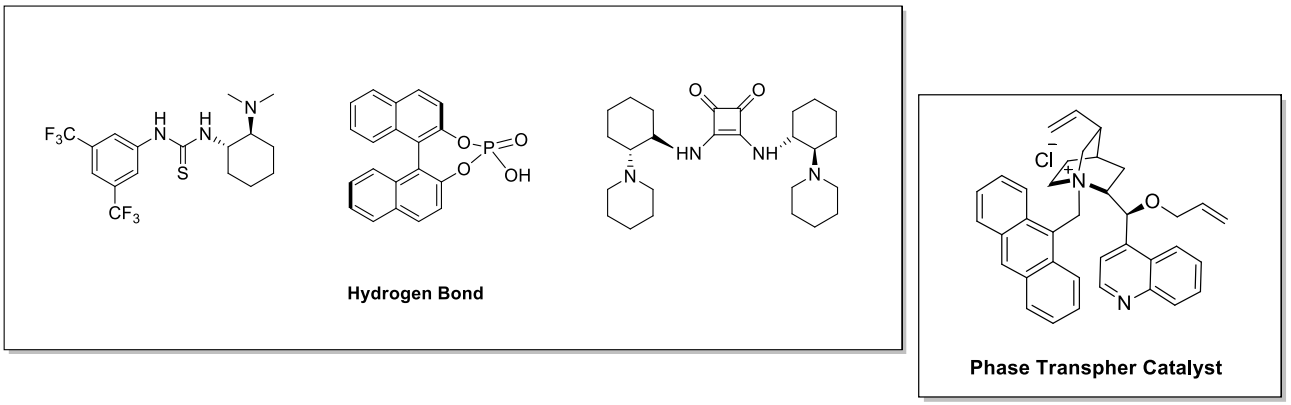


Figure 1.3.3

The development of synthetic pathways based on organocatalysis is becoming an effective strategy to face the issues represented by chirality in synthesis of novel heterocyclic molecules containing chiral centers in their scaffold. In fact, organocatalysis allows to develop one-pot or multistep reaction thanks to the large portfolio of catalytic system reported in literature in the past years.

For the absence of transition metals, organocatalytic methods are especially attractive for the preparation of compounds that do not tolerate metal contamination, such as biological active compounds, which could be hard to remove or give side reaction compromising structure and activity of compound.

1.4 Enantioselective synthetic routes to access heterocyclic compounds

Enantioselective synthesis of isoindolinones and phthalides attracted for years the attention of many research groups, especially for the possibility to asymmetrically functionalize carbon in 3-position of the heterocyclic ring systems.

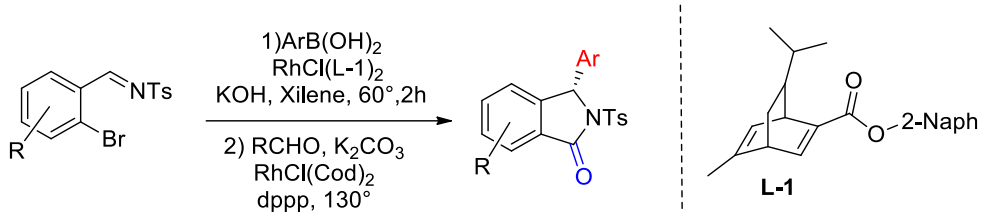
In the past decades, a certain number of asymmetric methodologies have been reported in literature, which use different catalytic systems and reaction conditions, based on both organocatalysis and transition-metal-catalysis, even though ineffective resolution of racemates has been widely utilized.

1.4.1 Catalytic asymmetric synthesis of isoindolinones

Beginning around 2010 particular emphasis has been put on transition-metal-catalyzed and organocatalyzed asymmetric synthesis to obtain such chiral lactam compounds.

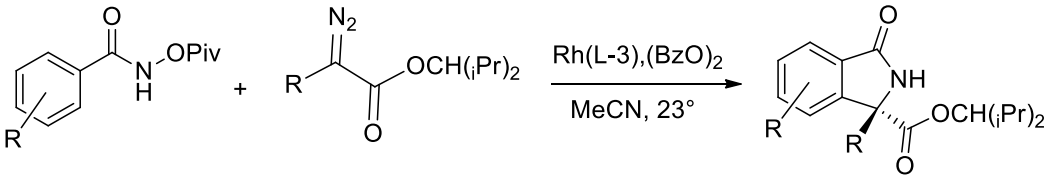
Transition-metal-complexes with chiral ligands used as catalysts in enantioselective synthesis of isoindolinones have been developed rapidly in past years, focusing on several transformations, including arylation, aza-Wacker cyclization, tandem Michael-Mannich reaction ecc.

Since 2012 many enantioselective procedures to afford phthalimidines using Rh(I) complex[19] have been developed. In this reaction, reported in the scheme **1.4.1,** the chiral metal complex catalyzes a sequence of asymmetric arylation/decarbonylation and aminocarbonylation, yielding the product in high ee.



Scheme 1.4.1

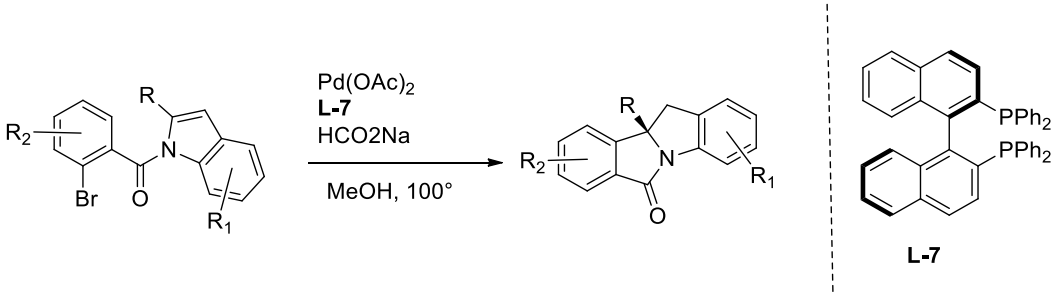
In 2014, Cramer[20] reported a highly enantioselective CpRh(III)-catalyzed C-H functionalization of phenyl hydroxamates with diazo esters to afford phthalimidines (**scheme 1.4.2**), investigating a very large range of Rhodium complexes, and Rh(**L-3**) displayed high catalytic activity, guiding the substrates by double facial selection, so the enantioselectivity depended on the size of substituent groups of the substrates.



Scheme 1.4.2

Chiral palladium complex catalysis has been explored to reach out enantioselective synthesis of isoindolinones and via aza-Wacker and Heck, in particular Heck reaction is representative for dearomatization of arenes even if mainly limited to anilines, indoles, pyrroles and phenols.

In 2015, the Jia's group reported an intramolecular dearomatization (**scheme 1.4.3**) of *N*-substituted indoles to afford isoindolinone scaffold[21].



Scheme 1.4.3

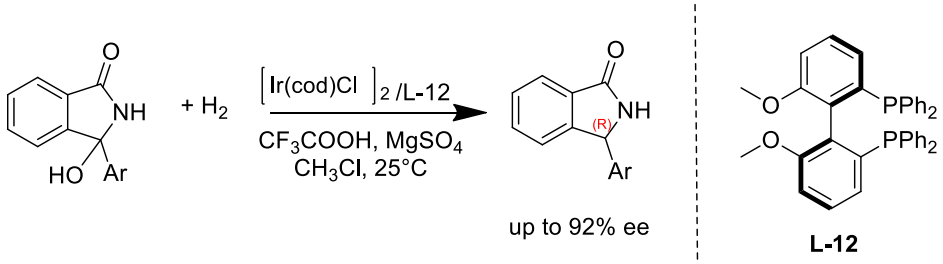
[19] M. Fujioka, T. Morimoto, T. Tsumagari, H. Tanimoto, Y. Nishiyama, K. Kakiuchi, *J. Org. Chem.* **2012**, *77*, 2911-2923.

[20] B. Ye, N. Cramer, *Angew. Chem. Int. Ed.* **2014**, *53*, 7896-7899.

[21] C. Shen, R. R. Liu, R. J. Fan, Y. L. Li, T. F. Xu, J. R. Gao, Y. X. Jia, *J. Am.Chem. Soc*. **2015**, *137*, 4936-4939.

A lot of substituted indoles bearing alkyl groups, ester or heteroaromatic groups, were well tolerated providing the final product albeit in modest yield with up 99% of ee.

This was a good strategy to achieve 3,3-substituted Isoindolinones, by dearomatization, but again the Jia's group, in 2017, developed an enantioselective hydrogenolysis of 3-aryl-3-hydroxyisoindolin-1-ones employing Ir(I) complex, to afford enantiopure 3-substituted isoindolinones[22](**scheme 1.4.4**).



Scheme 1.4.4

As showed in the previous examples, transition-metal-complex catalysis gave a very big contribution in synthesis of chiral 3-substituted isoindolinones, and this topic is still challenging.

Most of the reported examples were about the synthesis of 3,3-disubstituted isoindolinones, with limitations in construction of 3-substituted scaffold, often bearing aromatic rings in 3-position.

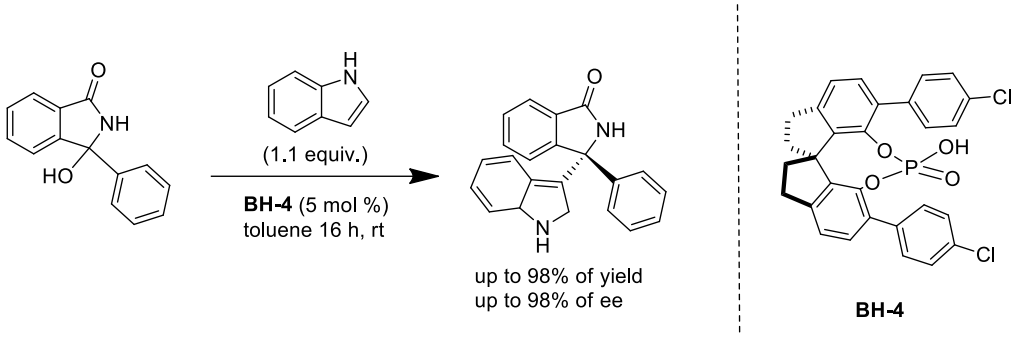
In order to overcome the limits of metal complexes catalysis, we will explore the contributions given by organocatalysis in synthesis of this particular kind of molecules in the past decades. The use of many catalytic system such as PTC or organocatalysts offered a very good alternative in synthesis of 3,3- or 3-substituted isoindolinones, in particular the development of one-pot, multistep and cascade reaction with a range of nucleophiles and electrophiles allowed to set up enantioselective synthesis of isoindolinone scaffold with the possibility to insert in exocyclic position different group of atoms such as N, O or S.

One important class of catalysts employed for this aim is chiral phosphoric acid. Generally, they have been employed to promote important transformations creating a chiral environment formed by an ion pair or hydrogen bond[23]. For this characteristic they are useful catalytic systems to synthetize 3,3-disubstituted isoindolinones from 3-hydroxy isoindolinones through formation of ketimine intermediates. Then, chiral phosphoric acid blocks one face of intermediate and on the other side, the nucleophile approaches to generate chiral 3-substituted isoindolinones.

[22] C. Ge, R. X. Liang, R. R. Liu, B. Xiang and Y. X. Jia, *Tetrahedron Lett.*, **2017**, *58*, 142-144.

[23] T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chem. Int. Ed.* **2004**, *43*, 1566-1568.

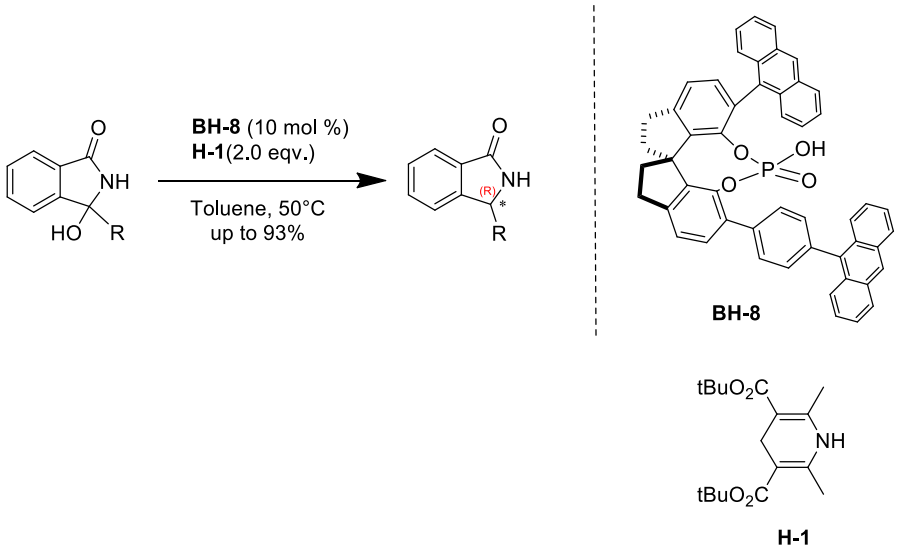
In 2017, You[24] and coworkers developed a good strategy to obtain chiral phthalimidines employing 3-hydroxylactams as starting material in reaction with indoles, under catalytic presence of chiral phosphoric acid, affording good yield and ee up to 98% (**scheme 1.4.5**).



Scheme 1.4.5

Iminium group was found sensitive to reduction by Hantzsch esters, so during last decades many research groups decided to use this good strategy to develop synthesis of 3-monosubstituted isoindolinones, limited to substrates with R=aromatic groups, employing this kind of esters in reaction with chiral phosphoric acids, gaining very interesting results.

In 2018[25], Shi group reported enantioselective synthesis of 3-substituted isoindolinones using SPINOL **BH-8** with Hantzsch esters obtaining ee up to 98% (**scheme 1.4.6**) and demonstrating one more time the versatility of this catalytic system in the synthesis of different substituted isoindolinones.

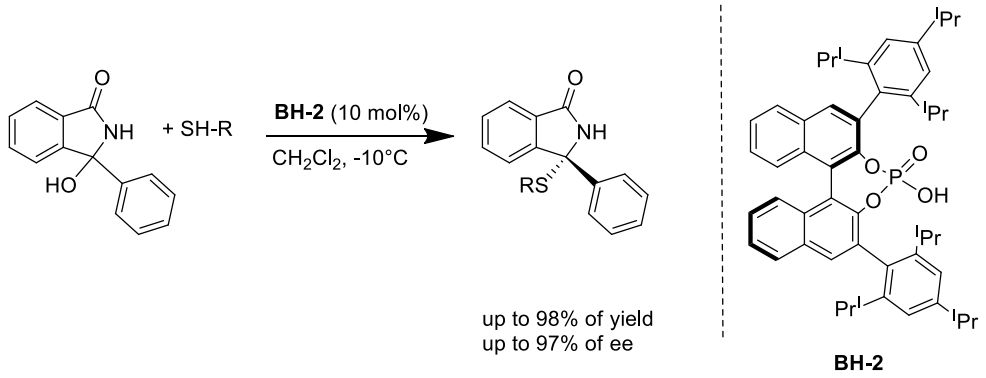


Scheme 1.4.6

[24] D. Glavač, . Zheng, . Dokli, S. . ou, M. Gredičak, *J. Org. Chem.* **2017**, *82*, 8752-8760.

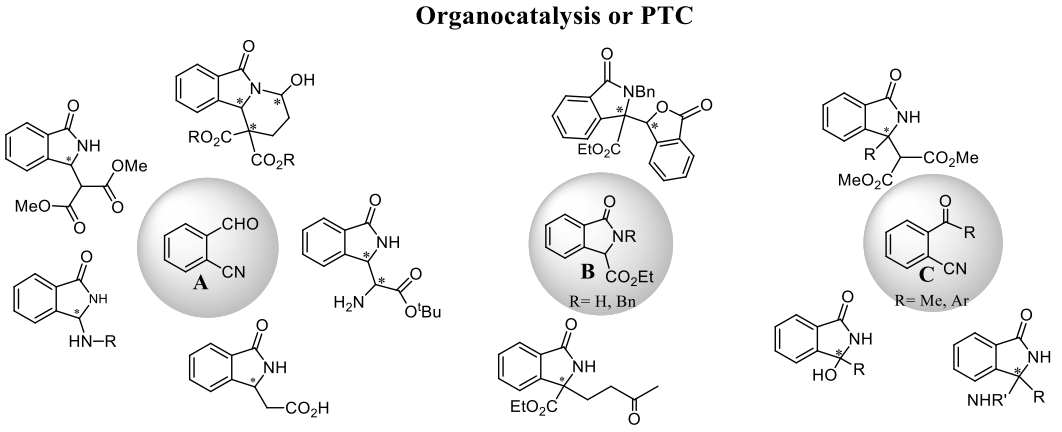
[25] Y. L. Zhang, L. He, L. Shi, *Tetrahedron Lett.* **2018**, *59*, 1592-1595.

Exploring the potential of chiral phosphoric acids in asymmetric synthesis of this class of molecules, we can't underline the great contribution of Gredičak group[26] in this field. The work of his group, allowed to use this system not only to synthetize enantioenriched 3,3-disubstituted isoindolinones (**scheme 1.4.7),** but also to insert in exocyclic position, for the first time, important heteroatom as sulfur group, the first example in this kind of chemistry, which underlines the great versatility of this catalytic system.



Scheme 1.4.7

In this field a great contribution for synthesis of enantioselective product was achieved using chiral phase transfer catalysts and thiourea catalysts. These classes of catalysts were found as a unique tool to synthetize 3- and 3,3-disubstituted chiral isondolinones developing simple operation and environment-friendly cascade processes under mild conditions. In the past 10 years, this topic especially investigated by our group, showed the potentiality and versatility of these catalytic systems, enabling to furnish isoindolinone scaffold with high selective processes and differently substituents with carbon and hetero group in exocyclic position. For the previous reason it's worthy to analyse the efforts put into this kind of chemistry (**Scheme 1.4.8**).



Scheme 1.4.8

[26] J. Suc, I. Dokli, M. Gredičak, *Chem Commun.* **2016**, *52*, 2071-2074.

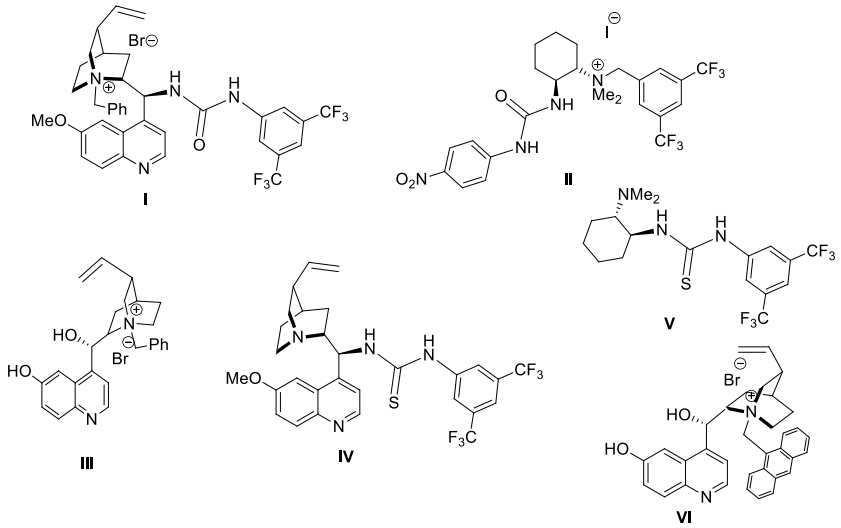


Figure 1.4.1

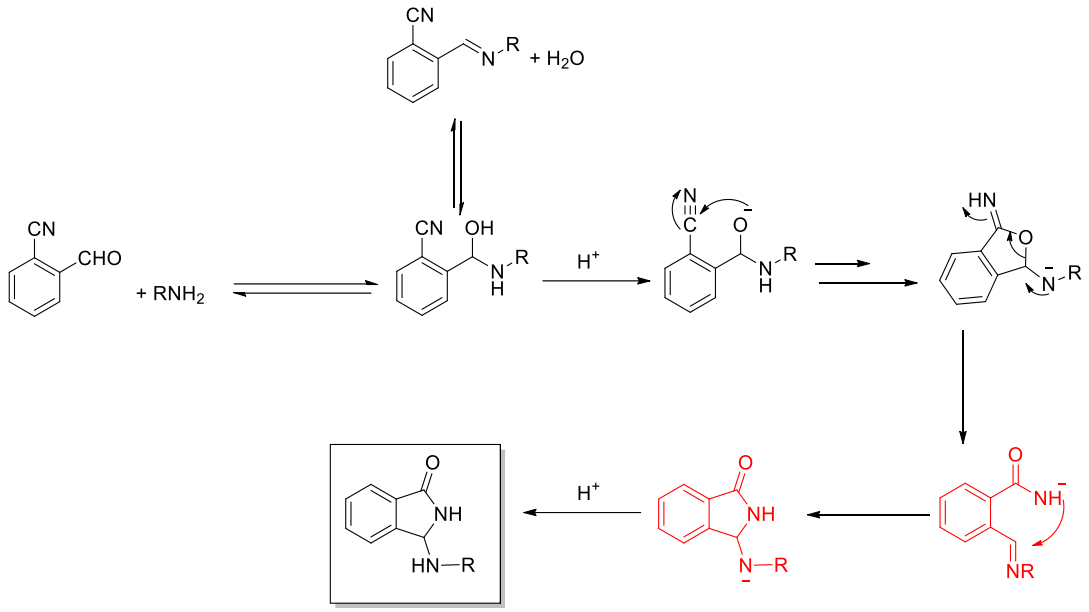
Already in 2012[27], our group reported an efficient cascade reaction of 2-cyanobenzaldehyde **A** with active methylene compounds to get chiral compounds in the presence of catalyst I under phase transfer catalysis, and consequent reaction with acrylaldehyde produced a fused ring compound. This reaction was a demonstration of the potential of this catalytic system in enantioselective synthesis of fused isoindolinones. To optimize the process, several ammonium salts were investigated with other activated methylene[28] compounds and the thiourea moiety was found as an essential prerequisite for the selectivity of the process.

The substrates scope was investigated, still by our group as in the enantioselective reaction of 2 - cyanobenzaldehyde and benzylamine, with bifunctional cinchona-derivative ammonium salt to obtain enantioenriched 3-monosubstituted isoindolinones. In this case amino benzyl moiety in exocyclic position was obtained[29], demonstrating one more time, the versatility of PTC in cascade reaction processes, also thanks to the work done in collaboration with professor Mario Waser in University of Linz (JKU).

[27] a) V. More, R. Rohlmann, O. G. Mancheño, C. Petronzi, L. Palombi, A. De Rosa, A. Di Mola and A. Massa, *RSC Adv.* **2012**, *2*, 3592-3595.
b) S. Tiso, A. Massa, *J. Heterocycl. Chem.* **2015,** *52*, 1570-1575.

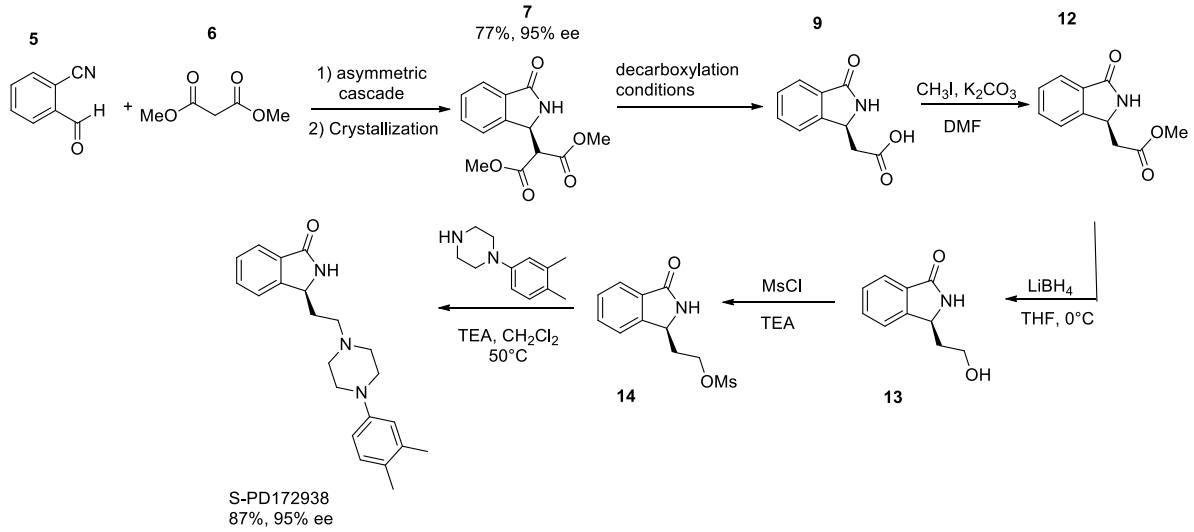
[28] A. Di Mola, M. Tiffner, F. Scorzelli, L. Palombi, R. Filosa, P. De Caprariis, M. Waser and A. Massa, *Beilstein J. Org. Chem.* **2015**, *11*, 2591-2599.

[29] A. Capobianco, A. Di Mola, V. Intintoli, A. Massa, V. Capaccio, L. Roiser, M. Waser, L. Palombi, *RSC Adv.* **2016**, *6*, 31861-31870.



Scheme 1.4.9

Further investigations were pioneered by our group about the potential of 2-cyanobenzaldehyde in synthesis of isondolinones, also employing bifunctional organocatalysts containing a thiourea moiety and a tertiary amine, such as catalyst **IV**, to obtain high enantioselective process. Catalyst **IV** (**figure 1.4.1**) was found essential to form enantioenriched 3-substituted isoindolinone in the reaction of cyanobenzaldehyde with β-ketoesters through tandem mechanism of rearrangement of the intermedium. In particular, the catalyst, with double activation of carbonyl group and deprotonation of nucleophilic nitrogen, performed an enantioselective closure of the product via intramolecular aza-Michael process, affording the final product with very good enantioselectivity of 78% ee, which was further increased to a remarkable ee of up to 99%[25] after a reverse crystallization. Because of the high enantioseletivity of the process with dimethylmalonate, the product was employed as a useful chiral building block to achieve smart synthesis of biologically active derivatives as (S)-PD172938 (**scheme 1.4.10**), potent dopamine D4 ligand, showing the multiple applications of this synthetic route also in pharmaceutical chemistry and related fields.



Scheme 1.4.10

This procedure has been also extended to analogue ketones of cyanobenzaldehyde, 2-acylbenzonitriles, in reaction with nitromethane and DMM to achieve respective 3,3-disubstituted isoindolinones bearing a methyl group in 3-position.[30-31].

Still concerning the field of thiourea catalyst, recently, we explored synthesis of hybrids with phthalides and isoindolinones containing contiguous stereocenters, employing thioureidic catalyst V, also known as Takemoto catalyst, and promoting cascade reaction, affording the desired product after mild hydrolysis of imidate intermediate. High enantioselectivity of the process has been observed also in this case, with ee up to 94%.

It's clear how the metal-complexes catalysis and the organocatalysis contributed to develop enantioselective synthesis of this class of molecules, and, organocatalysis contributed with many different catalytic systems, employing different starting materials to promote enantioselective cascade reactions to construct isoindolinones scaffold.

Despite the remarkably number of applications of 2-cyano benzaldehyde, until now not many routes have been explored for the synthesis of 3-substituted isoindolinones. Cascade reactions of 2-cyanobenzaldehyde showed several limitations themselves. In fact, it has been proved that nitromethane leads to a complex mixture of products, reactions performed with acetylacetone as nucleophile provide only racemic final product despite many catalytic systems have been tested in our lab in this kind of reactions. Heteronucleophiles such as thiols cannot be employed. Based on these assumptions, it's necessary the development of new catalytic processes linked to new designed starting materials suitable to go overcome these limitations.

[30] F. Romano, A. Di Mola, L. Palombi, M. Tiffner, M. Waser, and A. Massa, *Catalysts* **2019**, *9*(4), 327.

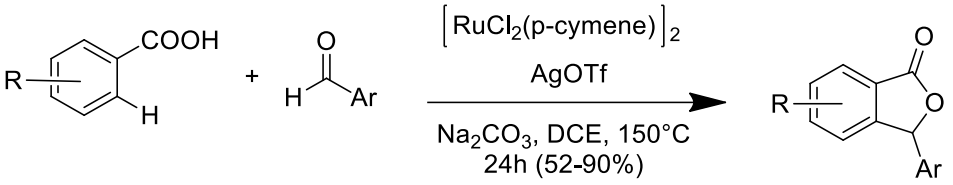
[31] G. Monaco, M. Tiffner, A. Di Mola, W. Herrebout, M. Waser, A. Massa, *Molecules* **2020**, *25*(10), 2272.

1.4.2 Catalytic asymmetric synthesis of Phthalides

As we previously underlined, also phthalides gained popularity in the past years, especially in organic synthesis and in pharmaceutical chemistry because of the wide range of activities of these compounds[32] such as in mental and cardiovascular diseases. In this paragraph the most recent advances in the synthesis of this class of molecules have been reported, with particular attention to asymmetric synthesis.

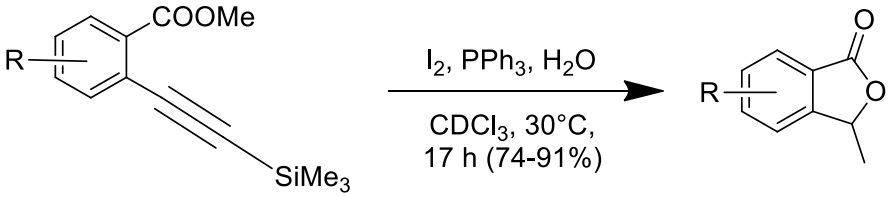
Generally, the routes to obtain such interesting compounds are divided in two class: racemic and asymmetric approaches.

A relevant example about the synthesis of 3-substituted phthalides has been reported by Fan and coworkers using ruthenium-catalyzed intermolecular cascade reaction (**scheme 1.4.11**). This synthesis involves insertion of the C-H bond of aromatic aldehydes followed by consecutive intramolecular nucleophilic substitution.



Scheme 1.4.11

The following procedure developed by Kawaguchi[33] eliminated the presence of metal complexes to form phthalides, furnishing 3-substituted phthalides in very high yields. The reaction proceeds with I_2, PPh_3 and H_2O in $CDCl_3$, through 4 step desilylation, hydro-iodination, cyclization and reduction, in one pot (**scheme 1.4.12**).



Scheme 1.4.12

Certainly, this kind of approaches is very interesting considering the mechanism of the reaction, but these procedures lead to non-selective synthesis of phthalides. Asymmetric synthesis of phthalides have been also reported.

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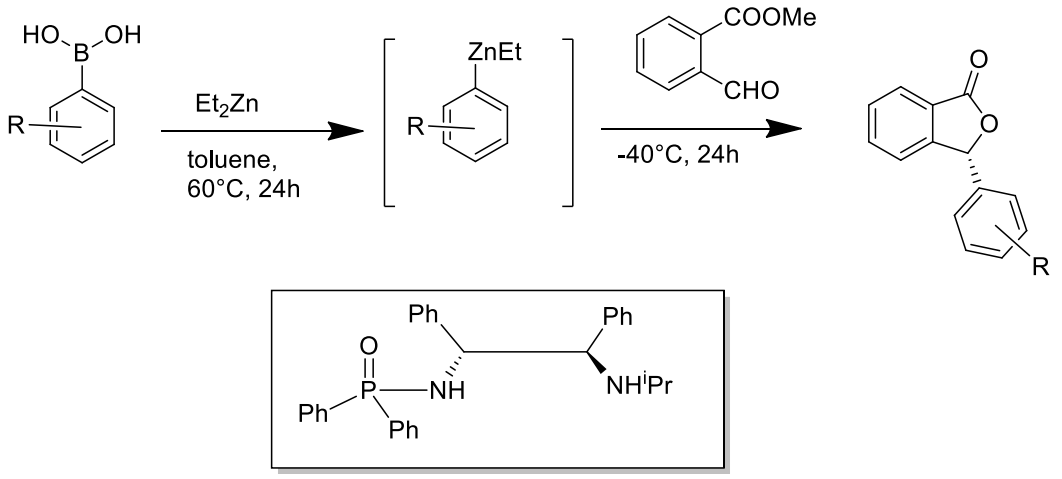
[32] R. Karmakar, P. Pahari and D. Mal, *Chem. Rev*., **2014**, 114(12), 6213.

[33] Kawaguchi, K. Nakamura, K. Yamaguchi, Y. Sato, Y. Gonda, M. Nishioka, M. Sonoda, A. Nomoto and A. Ogawa, *Eur. J. Org. Chem*., **2017**, 5343.

For what concerning the chiral metal complexes in synthesis of 3-substituted phthalides many examples have been reported in recent years.

Huang[34] and co-workers discovered a new protocol for the synthesis of chiral 3-substituted phthalides by 1,2-addition of methyl 2-formylbenzoates followed by lactonization, using a chiral phosphoramide ligand–Zn(II) complex (**scheme 1.4.13**). The efficiency of the process is highlighted by the fact that the enantiopure phthalides were obtained in excellent yield and good enantioselectivity up to 87%.

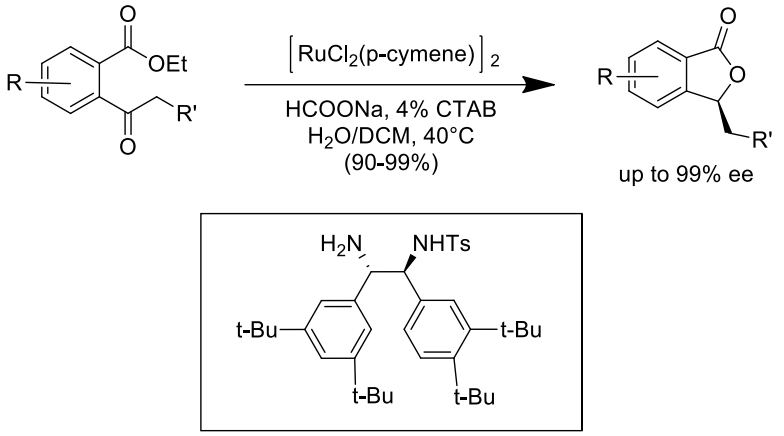


Scheme 1.4.13

One of the best results in synthesis of 3-substituted phthalides was reported by Zhang[35] and co-workers. This route goes through reductive cyclization of 2-acylarylcarboxylate via asymmetric transfer hydrogenation. The reaction was promoted by a new Ru (II)-diamine complex, which catalyzes selective hydrogenation and in situ lactonization to achieve enantiopure 3-substituted phthalides (**scheme 1.4.14**). The observed excellent enantioselectivity can be explained by a preferable transition state of the Ruthenium complex and ethyl 2-acylarylcarboxylate starting material, which determines the chirality. Hydrogen bonding with the near ester function group of the 2-acylarylcarboxylate substrate that might also be accountable for the observed selectivity.

[34] H. Huang, Y. Wang, H. Zong and L. Song, *Appl. Organomet. Chem*., **2019**, 33, e4643

[35] B. Zhang, M. H. Xu and G. Q. Lin, *Org. Lett.*, **2009**, 11, 4712.



Scheme 1.4.14

Metal complex catalysis has been found as good strategy to reach out 3-substituted phthalides, in terms of enantioselective or racemic procedure. The results gained with this type of catalysis, have been achieved mostly using harsh reaction condition. In spite of this consideration, it is good to investigate what was the contribution of other synthetic routes and catalytic system in this field, considering alternative strategies such as organocatalysis.

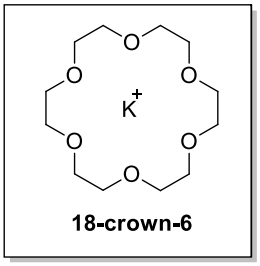
Also in this case, many representative examples are reported.

Recently many groups focused their efforts in developing new synthetic strategies to achieve enantioselective synthesis of phthalides involving different synthetic routes and catalytic system.

A great contribution to find out alternative pathways to pursuing the selective synthesis of 3 and 3,3 substituted phthalides avoiding chiral metal complexes, has been given from Della Sala and co-workers, which developed very effective routes for access this valuable class of compounds.

In 2019 Della Sala and his research group, in University of Salerno, reported the first diasteroselective synthesis of 3-substituted phtalides through arylogous Michael reaction promoted by catalytic amounts KOH/18-crown-6 catalyst in mesitylene in the presence of N,O-bis(trimethylsilyl)acetamide[36] (**Scheme 1.4.15**).

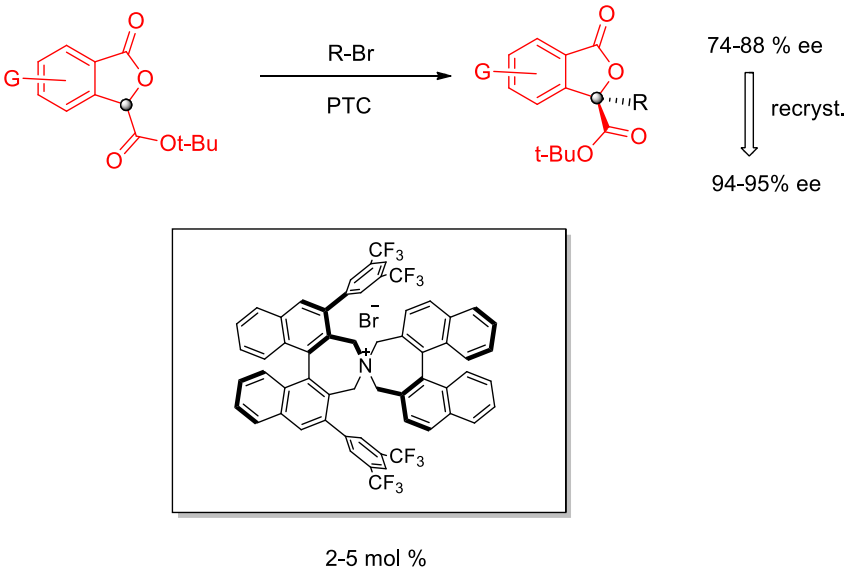
[36]M. Sicignano, R. Schettini, L. Sica, G. Pierri, F. De Riccardis, I. Izzo, B. Maity, Y. Minenkov, L. Cavallo, and G. Della Sala, *Chem. Eur. J*., **2019**, 25, 7131 – 7141



Scheme 1.4.15

This useful strategy constituted a very interesting example to achieve this class of compounds in good yield and good diasteroselectivity without use of metal complexes and extending the organocatalysis field in synthesis of phthalidic derivatives.

Still Della Sala group, in 2020 continued to explore the synthesis of phthalides through use of PTC to reach out new class of 3,3 substituted phthalides in excellent yield and selectivity[37](**Scheme 1.4.16**).



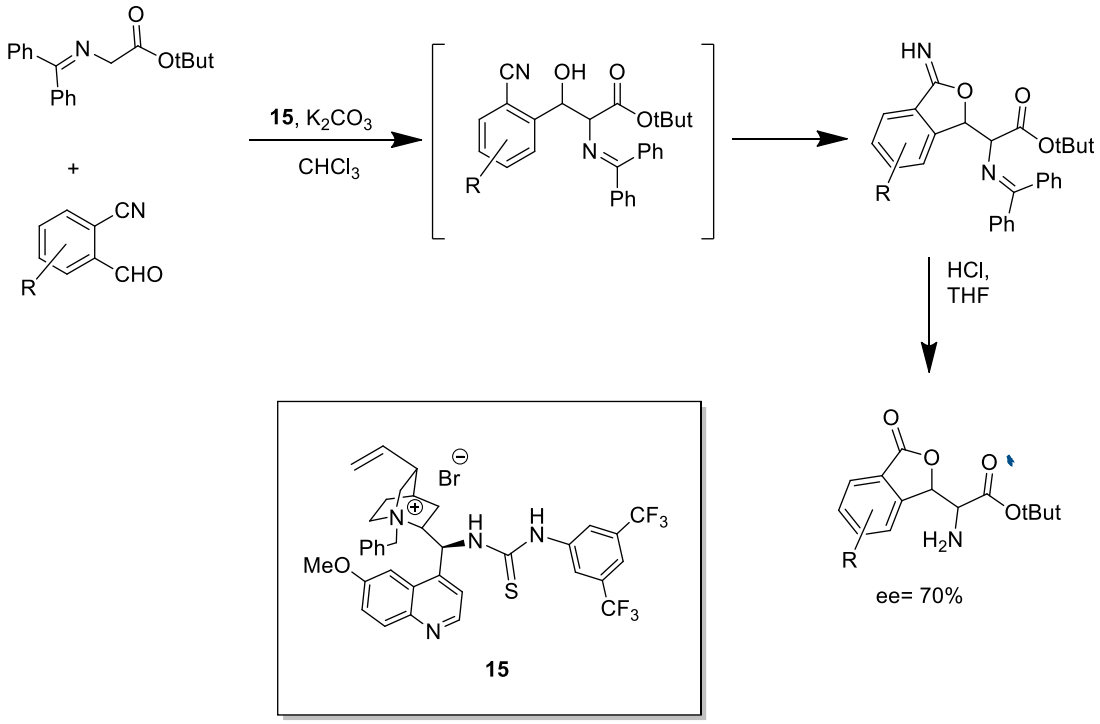
Scheme 1.4.16

As showed in the scheme, the reaction involves nucleophilic substitution with alkyl bromide group under the effect of PTC to give the corresponding tetrasubstituted phtalide with good level of yield and selectivity which can be easily increased after recrystallization. The carboxylic ester was found as important motif of selectivity of this synthetic pathway thank to ionic interaction between ester group and PTC.

[37] M. Sicignano, R. Schettini, G. Pierri, M. Leda Marino, I. Izzo, F. De Riccardis, L. Bernardi, and G. Della Sala, *J. Org. Chem.* **2020**, 85, 11, 7476–7484

These novel approaches are representative of the contribution of organocatalysis in synthesis of 3 and 3,3 substituted phtalides with excellent stereocontrol and good alternatives to conventional chiral metal complexes synthesis.

Still in the University of Salerno, in past years, gave good insights exploring different organocatalytic system and employing new starting materials in synthesis of this interesting class of compounds, In particular, in 2014 Massa[38] group developed a double routed cascade reaction employing new designed PTC catalyst in reaction with 2-cyanobenzaldehyde or 2-carbomethoxy benzaldehyde, gaining moderate results in terms of selectivity (**scheme 1.4.17**).

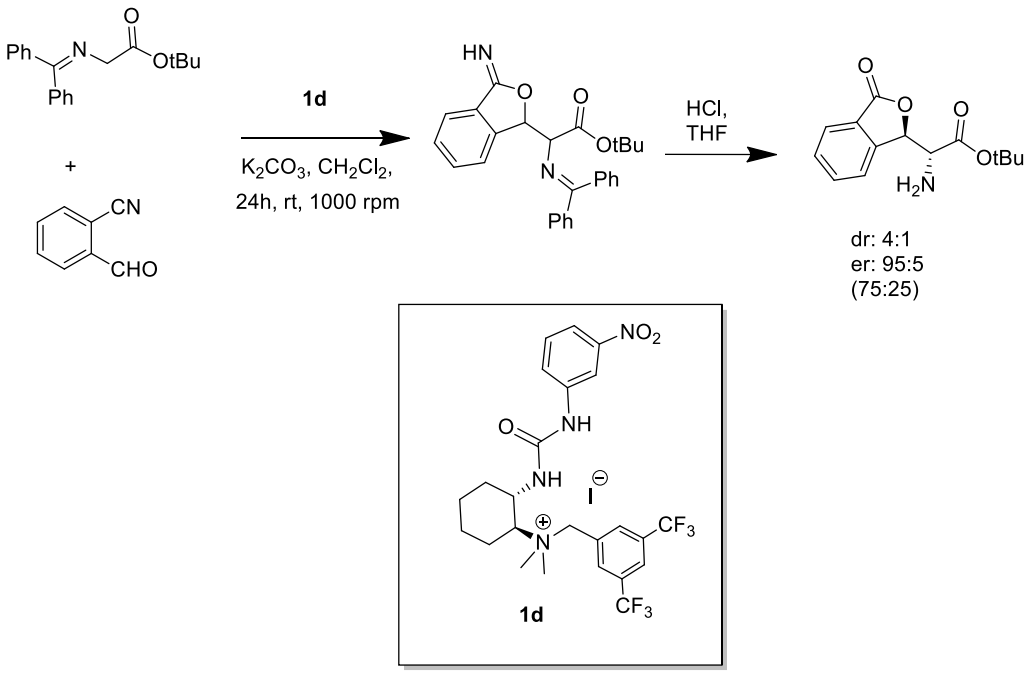


Scheme 1.4.17

Afterwards, this procedure was better investigated, thanks to work done in collaboration with University of Linz (JKU). Waser and Massa[39] designed new thiourea PTC able to achieve better results in terms of yield and selectivity, The use of catalyst **1d** produced good diasteroselectivity and good ee up to 90%, improving the previously reaction reported by our group (**scheme 1.4.18**).

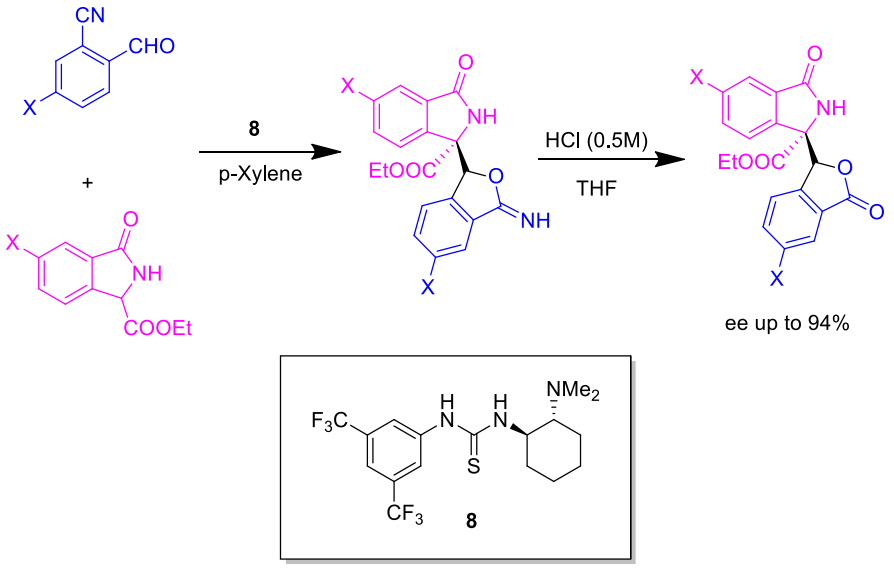
[38] M. Perillo, A. Di Mola, R. Filosa, L. Palombi and A. Massa, *RSC Adv*., **2014**, 4, 4239

[39] M. Tiffner, J. Novacek, A. Busillo, K. Gratzer, A. Massa and M. Waser, *RSC Adv.*, **2015**,5, 78941-78949.



Scheme 1.4.18

Investigation of other catalytic systems in the reaction with o-cyanobenzaldehyde continued to be the topic of study of our research group. In the construction of 3-substituted phthalides, thiourea catalysts were found very effective in synthesis of new hybrids with phthalides and isoindolinones[40], still using cascade reaction strategy (**scheme 1.4.19**).



Scheme 1.4.19

Clearly, 2-cyanobenzaldehyde was found an attractive building block for synthesis of 3-substituted isoindolinones, especially for the possibility to use mild conditions and cascade reaction with a wide range

[40] A. Di Mola, F. Scorzelli, G. Monaco, L. Palombi and A. Massa, *RSC Adv.*, **2016**,6, 60780-60786

of nucleophiles and to functionalize the exocyclic position, without several limitations. Therefore, organocatalysts and PTC have been discovered as efficient catalytic systems to carry out this synthetic pathway achieving 3-substituted phthalides as well in good yields and very high selectivity.

As we can see in the previous examples in the past decades several procedures have been developed to face the challenge of synthesis of phthalides, but protocols to reach out enantioenriched 3-substituted phthalides, are still ongoing. Many progresses have been done to face this challenge, but these procedures still got several limits, and the development of organocatalytic pathways it's been a good alternative for new easy access to this kind of molecules, especially for the role they play as biologically active compounds in heal of many important diseases. The procedures to obtain 3-substituted phthalides starting from 2-cyanobenzaldehydes are still under explored, and certainly deserve several more investigations to enlarge the range of possibilities of this class of molecules in many fields of chemistry and medicinal chemistry.

1.4.3 Synthesis of novel 3-isoquinolinones analogues.

1,4-Dihydro-3(2H)-isoquinolinones, also known as isoquinolin-3-ones form a very interesting class of compounds because these heterocycles display combination of aromaticity and saturation, an amide functionality, and several points of derivatization, some of which can also lead to chiral variants. Therefore, this core structure is responsible of biological activity in many related classes of compounds.

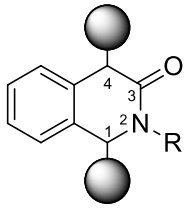


Figure 1.4.2

The possibility to functionalize the 4 and 1 position, makes this class of molecules very interesting from a synthetic point of view, but especially for what concerns the biological activity.

Their structure can be related to important molecules with very similar core structure, as isoquinolin-triones, active compounds in healing of contemporaneous issues as Alzheimer and ischemia as inhibitors of caspases, or tetrahydroisoquinolines (THIQs) from which they can be easily derived.

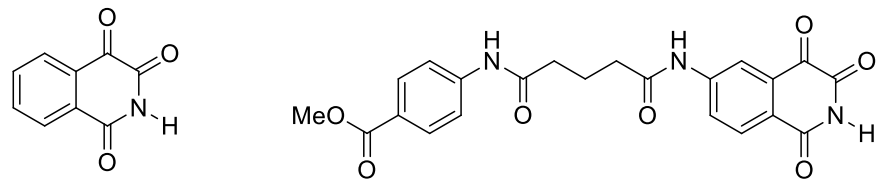
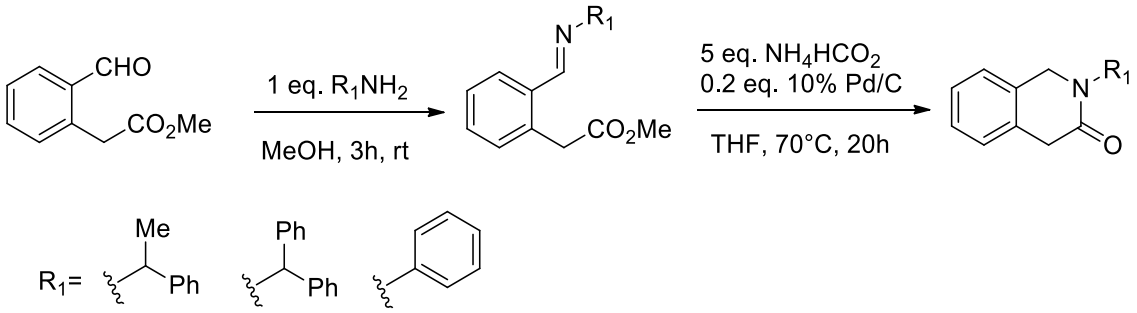


Figure 1.4.3

It is obvious that the isoquinolone scaffold can be suitable as good building blocks in synthesis of these active compounds, but further functionalization in 1 and 4 position can be used for design of new analogues of active molecules with unexplored biological activity.

Surprisingly, there are very few methods for the synthesis of 3-isoquinolinones.

In 2021, Richards[41] and co-workers developed a new facile access to the synthesis of new isoquinolinones via reductive amino/cyclization and subsequent α-carbonyl alkylation (**scheme 1.4.20**).

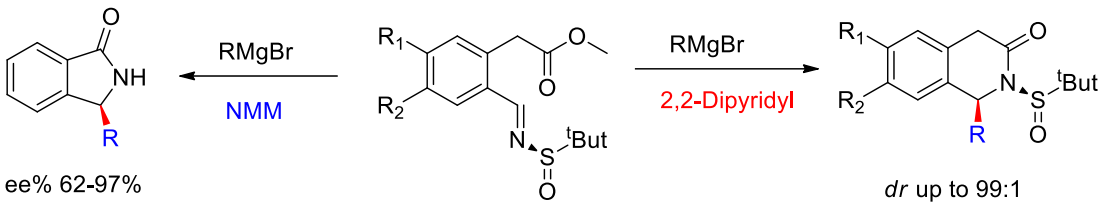


Scheme 1.4.20

In fact, the use of this particular kind of bifunctional imine could be very useful for developing further addition/cyclization processes in synthesis of more wide range of 3-isoquinolones.

Another example in synthesis of 1-substituted isoquinolones was reported by Wei and his research group, which developed a new synthetic route employing new bifunctional chiral imine in a one-pot cascade reaction[42].

[41] Michael J. O' Sullivan, Richard J.D. Hatley, Christopher R. Wellaway, Sean P. Bew, Christopher J. Richards, *Tetrahedron*, 100,(**2021**), 132455
[42] Wen Zhou, Yan-Xue Zhang, Xiao-Di Nie, Chang-Mei Si, Xun Sun, and Bang-Guo Wei, *J. Org. Chem.* **2018**, 83, 17, 9879–9889



Scheme 1.4.21

This strategy goes through selective addition of Grignard reagents to chiral imine followed by cyclization and producing very stereoselective closure leading to very high dr in the final product. Furthermore, easy deprotection and methylation of 2 position investigated by Wei group led to a facile access to (S)-(+)-cryptostyline, important ligand for dopamine receptor mostly employed in binding assays of D_1 receptor (**scheme 1.4.21**).

The use of this chiral imine was investigated as well in the synthesis of chiral isoindolinones with satisfying results in terms of selectivity.

It's important to underline how this strategy reported another example for synthesis of 1-substituted isoquinolones, giving new insights to investigating cascade reaction as useful strategies for synthesis of isoquinolone scaffold and their use as important building blocks in synthetic routes to access different derivatives with relevant meaning in pharmaceutical and biological fields.

2 Objectives

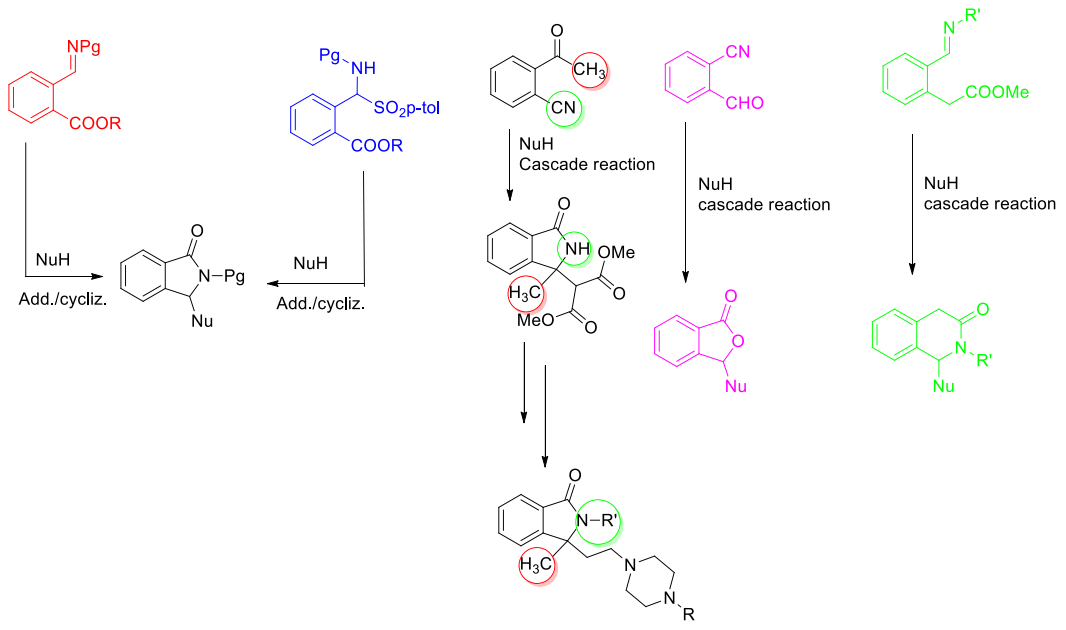
The aim of the thesis is the design of new starting materials containing groups enable to promote asymmetric cascade reactions, one-pot or also multistep reactions for synthesis of analogues of heterocyclic compounds of biological interest.

In particular, our attention focused on three classes of compounds structurally connected each other: isoindolinones, phtalides and 1-substituted isoquinolin-3-ones

The design of new starting materials in these cases is of paramount importance to overcome several limits in the synthesis of these heterocyclic compounds as highlighted in the introduction, developing efficient cascade type reactions and, in case of the introduction of new stereocenters, investigating asymmetric versions as well.

Particularly, this PhD thesis highlighted three main objectives:

1) Synthesis of tosylimine and α-amidosulphones derived from easily accessible 2-formyl benzoates, with the aim to develop new effective cascade reactions based on Mannich/lactamization process for constructing γ-lactam ring of isoindolinone scaffold. It is important to underline as these different strategies enabled to overcome several limits in previous synthetic routes of these kind of molecules inserting new side chain groups with very high enantioselectivity and yield.
2) Synthesis of imine analogs derived from 2-formylphenylacetates to better understand if the same synthetic pathways could be useful in construction of δ-lactamic rings of new isoquinolone structure.
3) The use of 2-cyanobenzaldehyde or 2-acetylbenzonitrile in cascade reaction to enable an easy access to synthesis of phthalides and isoindolinones analogues of biologically active products bearing tetrasubstituted stereocenters.



Scheme 2.1

3 Results and Discussion

New cascade reactions for synthesis of novel 3-substituted isoindolinones

Following what was mentioned in the objectives section 2 the first aim of the project regards the use of N-benzylidentosylimine derived from 2-formylbenzoate in reaction with thiols for enantioselective construction of 3-substituted isoindolinones with sulfur group and the investigation of mechanism of reaction which leads to the high selectivity observed in this process.

In section **3.3** the main topic will be particular the synthesis of α-amidosulfones also derived from 2-formylbenzoate and their use in asymmetric cascade reactions. We will focus our attention on the potential of this approach for easy access of 3-substituted isoindolinones functionalized with nucleophilic carbon group unreachable with synthetic routes previously mentioned.

In section **3.4** we discuss the total syntheses of novel 3-methylated analogs of Pazinaclone, the relevant biological effects of this class of isoindolinones in the treatment of several mental diseases.

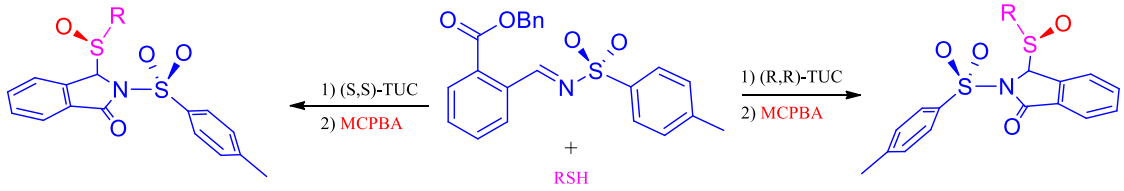
The **3.5** paragraph describes the stereoselective synthesis of novel masked β-amino acid containing phthalide developing a new application of 2-cyanobenzaldehyde. This project was carried out in collaboration with Prof. Mario Waser from University of Linz (JKU), during mobility period linked with PhD course.

Lastly, the section **3.6,** we investigate the reactivity of the homolog imine derived from 2-formylphenylacetate in nitro Mannich initiated cascade reaction/lactamization for the synthesis of novel isoquinolone scaffold.

3.1 2-Carbobenzyloxy N-tosylbenzylidenimine in enantioselective cascade reaction with thiols and following sulfoxidation.

A highly stereoselective synthesis of 3-sulfinyl- substituted isoindolinones has been achieved using tandem organocatalyzed addition/cyclization reaction of the new 2-carbobenzyloxy N-tosylbenzylidenimine with thiols, followed by diastereoselective oxidation with MCPBA[43].

The enantioenriched isoindolinone containing N,S-acetal moieties have been accomplished through a dynamic kinetic resolution promoted by a bifunctional chiral thiourea organocatalyst. The newly created carbon stereocenter enabled to led subsequent sulfoxidation with high diastereocontrol.

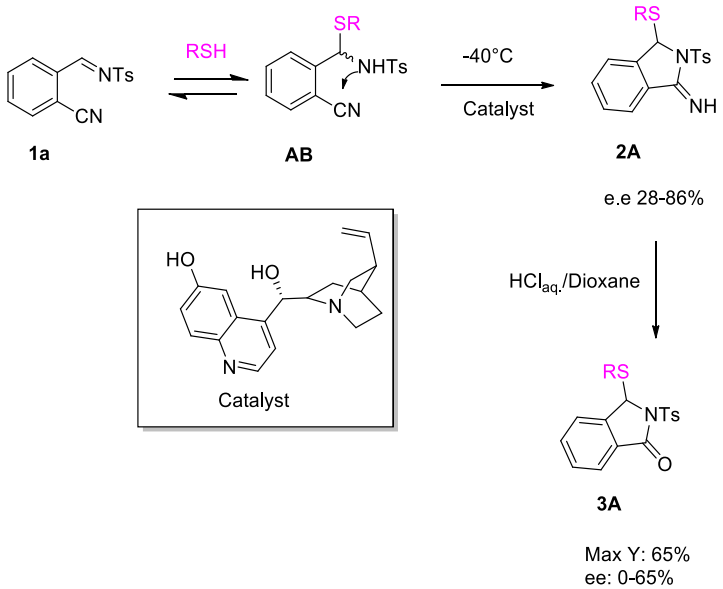


Substrate scope: R= Aryl, Alkyl, Alicyclic, functionalized Alkyl
Enantioselectivity: up to 98% ee

Scheme 3.1.1

3.1.1 Background

The synthesis of isoindolinone derivatives containing a thioether fragment in the C3 position is particularly challenging. We had only mediocre results developing a two-step shown in the following scheme.



Scheme 3.1.2

[43] L. Serusi, A. Massa, C. Tedesco, A. Capobianco, and L. Palombi. *J. Org. Chem.* ***2021***, 86, 10630−10639

The reaction involved the addition of RSH to the imine **1a**, a dynamic asymmetric transformation of the intermediate, and consequent hydrolysis of the isondolidin-imine **2A.**

Even if a first enantioselective attempt, to achieve these interesting derivatives, has been reported by our group, several drawbacks invalidated the procedure: the enantioselectivity of the entire process is strictly influenced by the nature of the thiol employed for this purpose (indeed, just acceptable enantiomeric excesses were reached using aryl thiols with EWG on the aromatic ring, or using benzyl-, alicyclic-, and sterically hindered aromatic thiols). But the most important thing is the product **2A** were found to be chemically and configurationally unstable compound. This represents the most significant problems considering that the hydrolysis reaction require very harsh condition (high temperature or microwaves) and long reaction times. These results persuaded us to explore other direct access to isoindolinone N,S-acetals operating structural modifications on the starting material and developing a new organocatalytic system for the reaction with thiols.

So, we elaborated an easy access to a new class of enantioenriched 3-sulfinyl-substituted isoindolinones by stereoselective oxidation of the exocyclic sulfur atom.

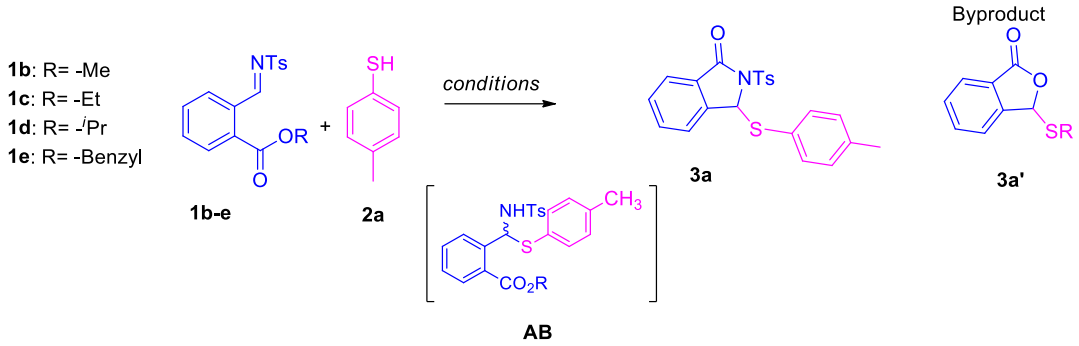
3.1.2 Results and Discussion

For instance, we focused all our efforts synthetizing carbo-alkoxy-tosylimine **1b**, for employing it on reaction with model thiol **2a,** under various experimental conditions and catalytic systems.

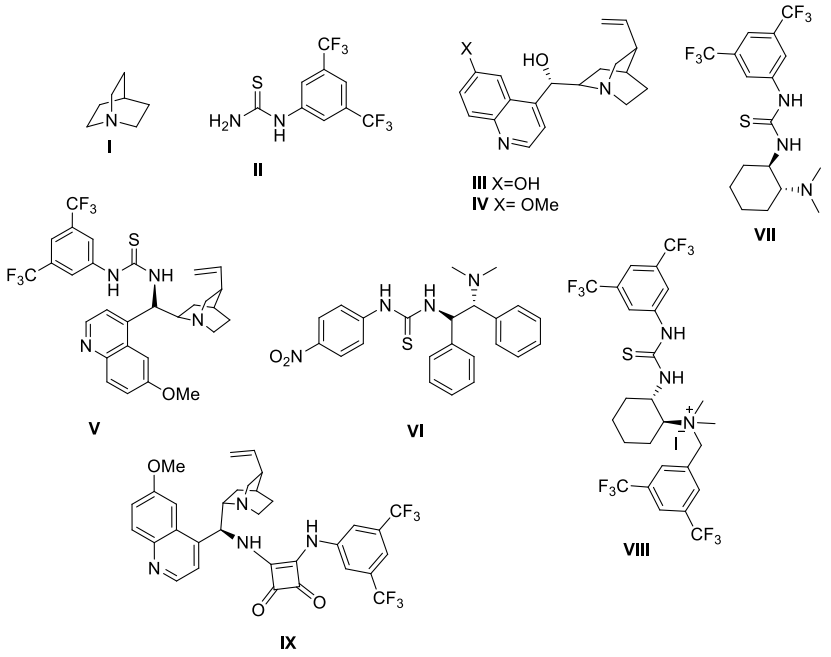
As we can see in the following table, in particular in the entry 1, 2, 3 and 4 (**table 3.1.1**), no product was gained carrying out the reaction with only tertiary achiral amine or thiourea or combining them. Some organocatalysts as quinidine and cupreidine (entry 4 and 5, **table 3.1.1**) were found also helpless or poorly effective.

As showed in the table, we were able to select as more helpful imine the **1e**, and the bifunctional thiourea **VII** as the best starting material and catalyst to lead the product **3a** with good yield and very high ee (entry 20). It's good mentioning that the benzyl ester functionality not only increase the selectivity of the process, but also it plays an essential role reducing the formation of the phthalide byproduct due to reaction between thiol and the aldehyde, which formed by partial hydrolysis of starting material in the reaction mixture.

Screening of Carboalcoxy-Imines, Catalysts and Conditions



Scheme 3.1.3



entry	1	catalyst (15%)	solvent/(mL/mmol)	reaction *t* (h)/*T* (°C)	3a	
					yield (%)	ee (%)
1	1b	Et_3N	DCM (1)	48/35		
2	1b	**I**	DCM (1)	48/35		
3	1b	**II**	DCM (1)	48/35		
4	1b	Et_3N/II	toluene (1)	48/50		
5	1b	**III**	toluene (1)	48/50		
6	1b	IV	toluene (0.9)	70/rt	16	36 (*R*)
7	1b	V	toluene (0.9)	17/rt	50	68 (*S*)
8	1b	VI	toluene (0.9)	48/rt	19	46 (*R*)

9	1b	VII	toluene (0.9)	40/rt	39 (43)	74 (*S*)
10	1b	VII	mesytilene (0.9)	21/50	62 (25)	78 (*S*)
11	1b	VII	DCM (0.6)	72/rt	35 (43)	69 (*S*)
12	1b	VII	DCM/Et_2O (1/2 0.9)	48/50	47 (25)	74 (*S*)
13	1b	VII	C_6H_5Cl (0.9)	40/50	40 (31)	77 (*S*)
14	1b	VIII/K_2CO_3	toluene (1.2)	24/rt	43 (12)	23 (*R*)
15	1b	IX	toluene	48/50	70	67 (*R*)
16	1c	VII	toluene (1)	90/rt	62 (35)	82 (*S*)
17	1d	VII	toluene (1)	90/rt		
18	1e	VII	toluene (1)	62/rt	79 (<5)	88 (*S*)
19	1e	VII	toluene (1)	64/−20	68 (15)	90 (*S*)
20	1e	VII	toluene (0.9)	42/rt	83 (<5)	88 (*S*)
21	1e	*ent*-VII	toluene (0.9)	48/rt	85 (<5)	87 (*R*)

Table 3.1.1

The reaction proceeds smoothly with both aromatic and non-aromatic thiols, demonstrating a robust tolerance of substrates and substituents in terms of enantioselectivity. Very good selectivity was observed with aromatic substrates bearing both EWG or EDG groups, as well with sterically hindered, alicyclic, and functionalized thiols. Conversely, heteroaryl thiols, such as 6-methoxybenzothiazole-2-thiol, were found completely ineffective in this reaction.

Scheme 3.1.4

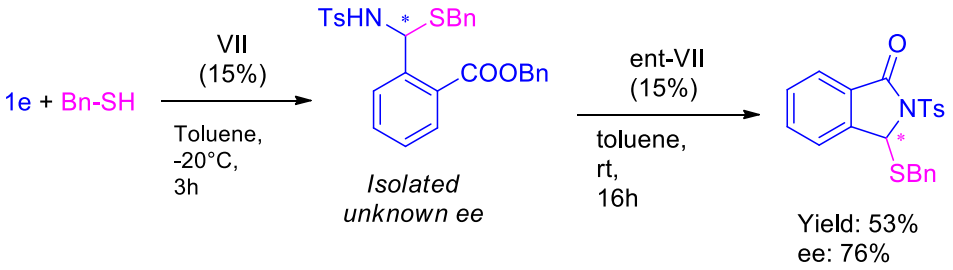
entry	R	reaction time (h)	(S)-3	yield (%)	ee (%)
1	4-MeO-phenyl (2b)	26	3b	80	95
2	4-MeO-phenyl (2b)	17	3b	60	85
3	4-MeS-phenyl (2c)	27	3c	50	87(87)
4	4-Br-phenyl (2d)	18	3d	59	88(89)

5	2-naphtyl (2e)	41	3e	48	83(86)
6	1-naphtyl (2f)	28	3f	52	94(94)
7	3,4-dimethyl-phenyl (2g)	31	3g	43	88(87)
8	2,5-dimethyl-phenyl (2h	31	3h	70	91(92)
9	benzyl (2i)	18	3i	84	85(81)
10	benzyl (2i)	40	3i	80	80
11	benzyl (2i)	64	3i	90	70
12	4-methoxybenzyl (2j)	26	3j	91	84(81)
13	2-phenylethyl (2k)	48	3k	55	82(82)
14	cyclohexyl (2l)	28	3l	61	94(92)
15	CH_2CO_2Me (2m)	18	3m	83	86(86)
16	$CH_2CH_2CO_2Me$ (2n)	22	3n	90	80(79)

Table 3.1.2

Unlike what was observed for the aromatic thiols, several NMR experiments showed that less acidic thiols add to imine only in the presence of the catalyst. To prove if the catalyst exerted control during addition step or, as we noticed for the aromatic thiols, through kinetic dynamic transformation, we performed a control experiment. We carried out the reaction with catalyst **VII** at -20°C to have a slow addition of the mercaptan to imine, then we isolated rapidly the intermediate from the crude mixture. Any attempt to determinate ee of the product was useless, so after rapid purification, we redissolved in toluene the intermediate, and left reacting in presence of catalyst **ent-VII**.

The enantioselectivity of the reaction clearly indicated the catalyst acts like as a chiral receptor of the intermediate leading to preferential closure of one enantiomer, enabling stereoinversion of the other one.



Scheme 3.1.5

In practice, the imine goes through spontaneous racemic adduct, the following cyclization via DKR, induced by catalyst, with contemporaneous activation of nucleophilic –NHTs and electrophilic –COOR, produces enantioselective formation of isoindolinone scaffold. The proposed transition states are as follows: when the racemic adduct is formed, interaction between one of two enantiomers promote the enantioselective closure

of one of two enantiomers through contemporaneous deprotonation of –NHTs by the tertiary base catalyst group and activation of electrophilic carbonylic group mediated by hydrogen bonding with the thiouredic group contained in the catalyst scaffold.

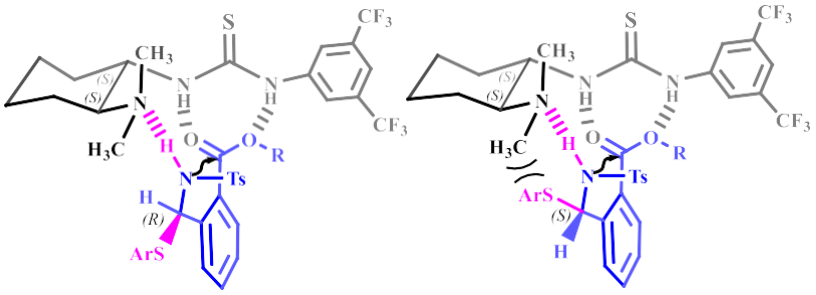
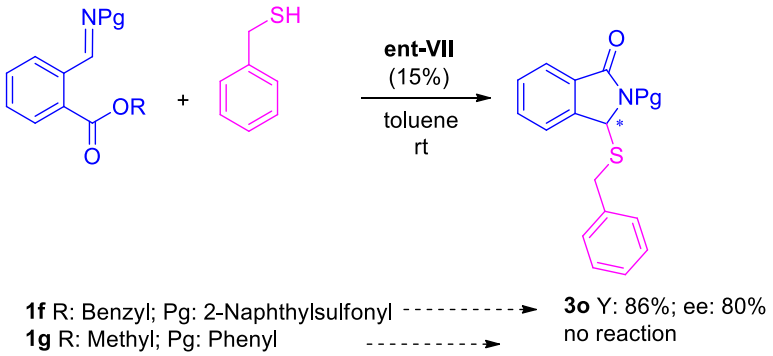


Figure 3.1.1

Otherwise, it's good to underline how the presence of sulfonyl protecting group is meaningful for the selectivity of the reaction. In fact, if the imine **1f (scheme 3.1.6)** furnishes the expected product in good yield and high ee, on the contrary, the imine **1g (scheme 3.1.6)** was found completely ineffective.

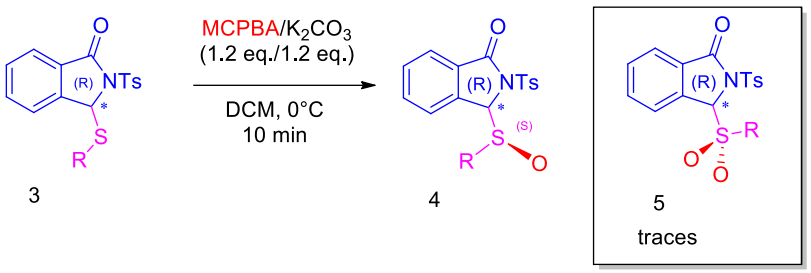


Scheme 3.1.6

This process triggered additional experiments about synthesis of isoindolinones containing other valuable functionalities at the exocyclic position.

In particular, our attention focused on the possibility to have a chiral sulfinyl moiety directly connected to the heterocyclic nucleus. Such a molecular structure could be attractive for further application in many other fields as medicine, being easily related to potentially bioactive compounds, substrates for other functionalization, N/S ligands for asymmetric catalysis etc.

Concerning this further investigation of second reactivity of this new class of compounds, by rapid screening, we were pleased to find that cheap, available MCPBA furnishes a very high chemo- and diasteroselective oxidation of the exocyclic sulfur atom to sulfoxide, under mild condition and short reaction time (**scheme 3.1.7**)



Scheme 3.1.7

entry	R	3	3 ee (%)	4	4 yield (%)	4 ee (%)
1	4-Me-phenyl	(*S*)-3a	88	(C_S,S_R)-4a	86	86
2	4-Me-phenyl	(*R*)-3a	46	(C_R,S_S)-4a	88	46
3	4-Br-phenyl	(*S*)-3d	88	(C_S,S_R)-4d	77	86
4	4-Br-phenyl	(*R*)-3d	89	(C_R,S_S)-4d	75	86
5	benzyl	(*S*)-3i	84	(C_S,S_R)-4i	86	82
6	benzyl	(*R*)-3i	81	(C_R,S_S)-4i	86	78
7	cyclohexyl	(*S*)-3l	96	(C_S,S_R)-4l	88	96
8	cyclohexyl	(*R*)-3l	99	(C_R,S_S)-4l	88	99

Table 3.1.3

Using 1.2 eqv. of MCPBA and an equal amount of K_2CO_3, only traces of the sulphonyl derivative could be detected, while the sulfinyl derivative has been achieved in high isolated yield, as a single diasteroisomer, in fact the ee of the sulfinyl compounds are mostly in line with the ones of the starting materials.

Further X-ray analysis on crystals of compound **4d**, revealed finally the absolute configuration of the new formed chiral center. So, we assumed the new chiral center can lead to selective formation of only one disteroisomer, underling the importance of the asymmetric carbon in 3-position in this process.

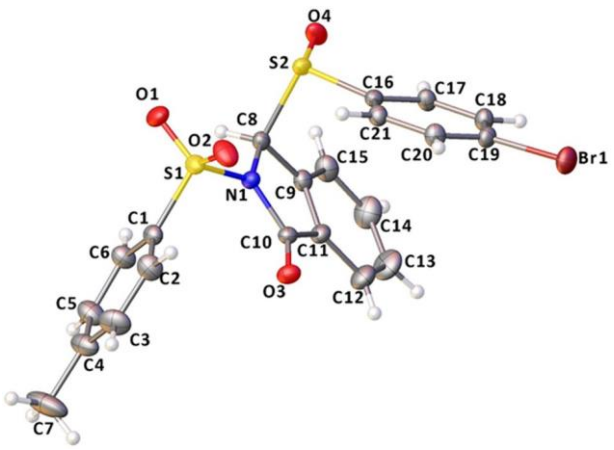


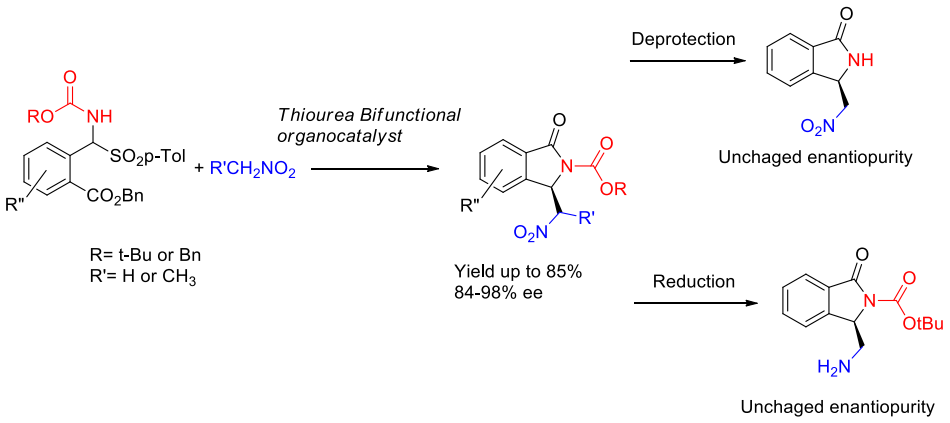
Figure 3.1.2

3.1.3 Conclusions

In this part we developed two very high stereoselective reactions that allows access to new enantioenriched 3-sulfinyl-substituted isoindolinones containing adjacent carbon and sulfur stereocenters. This reaction proceeds with good tolerance of synthetically useful functional groups. X-ray analysis in the new formed stereocenter, allowed to identify the absolute configuration of the formed sulfoxide underlining the importance of the new formed asymmetric center in leading the formation of only one diasteroisomer.

3.2 α-Amidosulfones: asymmetric cascade reaction for the synthesis of 3-(nitromethyl)isoindolin-1-ones

In this part, a new approach in the asymmetric synthesis of 3-substituted isoindolinones through the synthesis of new α-amidosulphones, designed from 2-formyl benzoates, has been described[44]. A new cascade reaction has been developed based on the asymmetric nitro-Mannich reaction of the α-amidosulphones, followed by in situ cyclization of the intermediate. Under the effect of a bifunctional thiourea organocatalyst, the Takemoto's catalyst, we developed a highly enantioselective process with ee up to 98% in good yield. Further investigation of the new obtained target, as selective Boc deprotection and reduction of nitro group, will be also the topic of this chapter.



Scheme 3.2.1

3.2.1 Background

After the first important goal represented by the development of organocatalytic addition of thiols to N-tosylimine derived from 2-formylbenzoate, we decided to move on investigating new potential starting materials suitable in this kind of reactions.

In facts, even if we found out that tosyl group is essential for the good selectivity of the protocol, any attempts to remove the tosyl group led to very disappointing results, and furthermore we noticed the N-tosylimine was unreactive with other kind of nucleophiles such as Acetylacetone, nitromethane and secondary amines. Some attempts carried out with the use of dimethyl malonate led to the final product only racemic and in very low yield.

[44] L.Serusi, L. Palombi, G. Pierri, A. Di Mola, and A. Massa, *J. Org. Chem.*, **2022**, 87, 13, 8420–8428

Therefore, we decided to attempt the syntheses of different starting materials bearing N-Boc or N-Cbz protecting groups. This alternative synthesis of imines of 2-formylbenzoates with N-Boc or N-Cbz protecting group, has never been reported in literature[45-46].

The easy synthetic pathway to access N-carbamoyl-α-amidosulfones and their relative stability led to several advantages, for instance avoid of using of the preformed imines, which can be unstable or difficult to isolate. The N-Boc imines can be formed easily in situ with the use of inorganic base. In fact, the use of this type of strategies has been explored, especially with the use of PTC and has been described in several past works with unsubstituted aromatic α-amidosulphones [47-48-49].

The use of aromatic α-amidosulphones functionalized in ortho position with a carboxylic group could be a viable synthetic route to achieve 3-substituted isoindolinones. The presence of the N-Boc or N-Cbz can be particularly useful for several further manipulations. The first aim of the project regards the synthesis of these new starting materials which have never been reported in literature. Then, we focused our attention on the possibility to develop an asymmetric nitro-Mannich reaction, an important tool for synthesis of many pharmaceutical ingredients and biological active compounds. It is worthy to note that the synthesis of isoindolinones, substituted in 3-position with a nitromethyl side chain, has never been reported, not even as racemate. Therefore, we investigated an asymmetric version of the designed reaction by using of organocalysis.

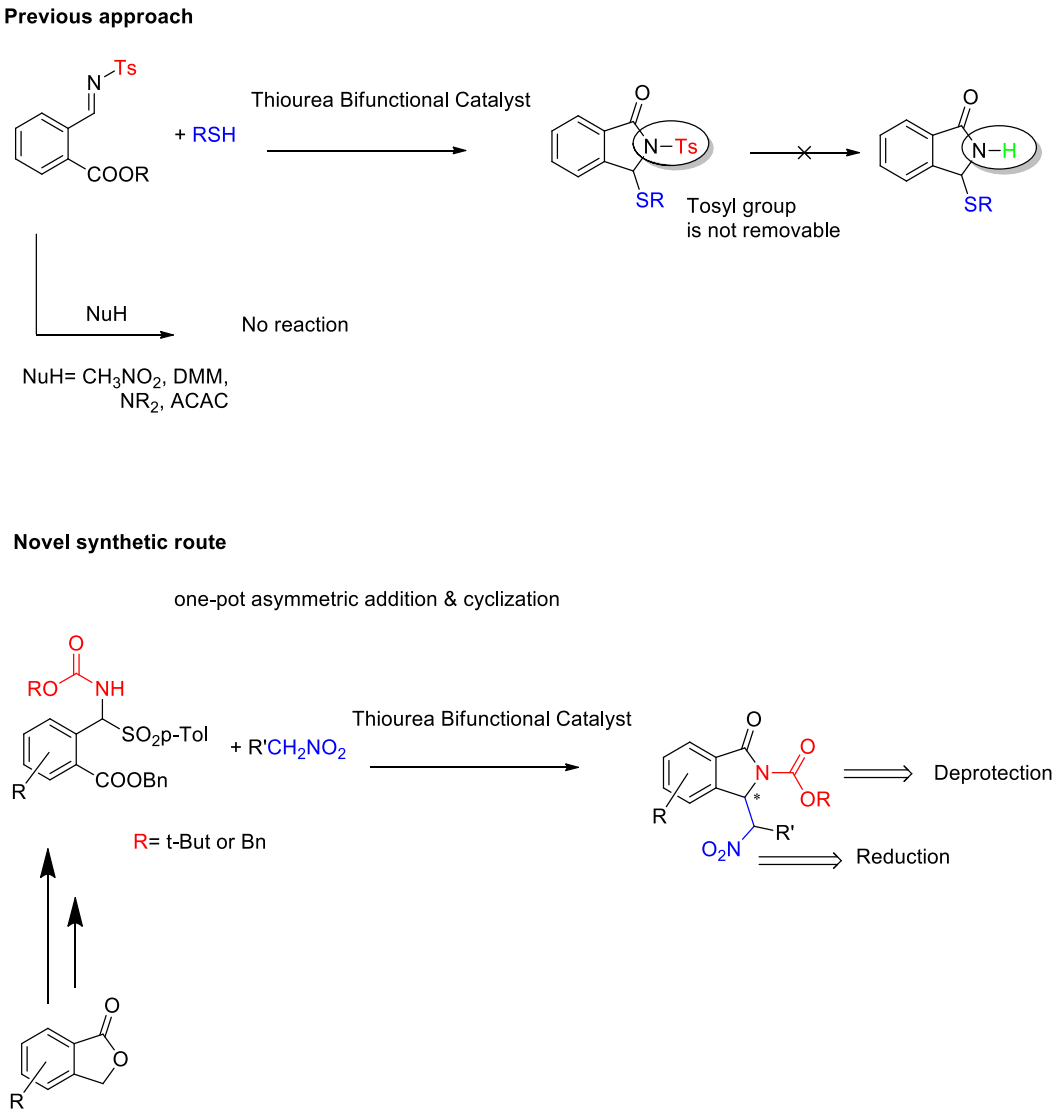
[45] Wang, Z. Q.; Feng, C. G.; Xu, M. H.; Lin, Q. C.**,** *J. Am. Chem. Soc*., **2007**, 129,5336−5337

[46] Guo, S.; Xie, Y.; Hu, X.; Xia, C.; Huang, H., *Angew. Chem*., Int. Ed. **2010**, 49, 2728−2731

[47] Fini, F.; Sgarzani, V.; Pettersen, D.; Herrera, R.; Bernardi, L.; Ricci, A., *Angew. Chem*., Int. Ed. **2005**, 44, 7975−7978.

[48] Palomo, C.; Oiarbide, M.; Laso, A.; Lopez, R., *Am. Chem. Soc*., **2005**, 127 (50), 17622−17623.

[49] Gomez-Bengoa, E.; Linden, A.; Lopez, R.; Mugica- Mendiola, I.; Oiarbide, M.; Palomo, *J. Am. Chem. Soc*., **2008**, 130 (25), 7955−7966.

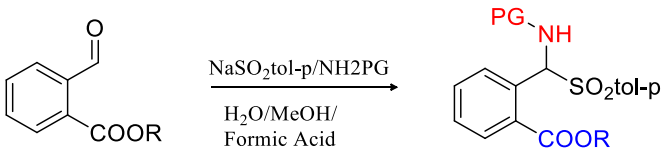


Scheme 3.2.2

3.2.2 Results and Discussion

First, we synthetized α-amidosulphones in >2mmol scale to demonstrate that starting material could be easily achieved and isolated, adapting a procedure reported in literature[50] (**Scheme 3.2.3**). The reaction goes through iminium intermediate to form the respective amidosulphones which precipitate in reaction mixture and can be easily isolated filtering and washing with water and ether.

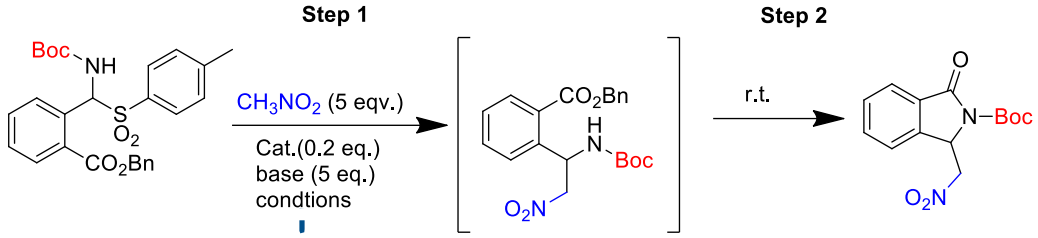
[50] A. Louise Tillman, J. Ye and D. J. Dixon, *Chem. Commun.*, ***2006***, 1191–1193



PG= Boc, Cbz
R= Bn, Me

Scheme 3.2.3

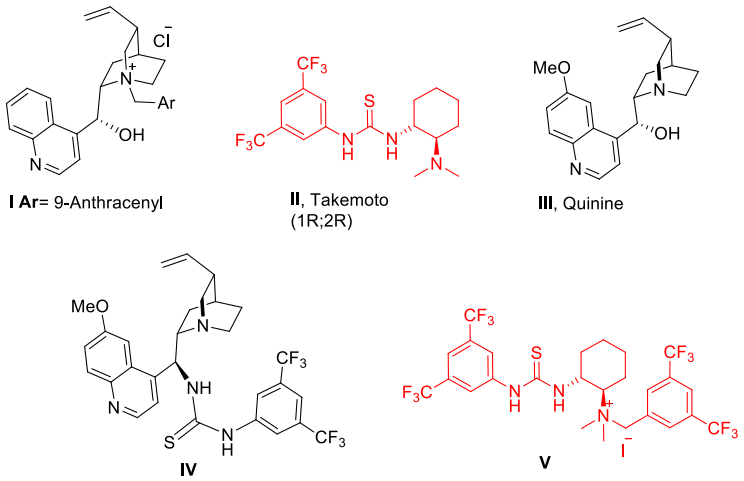
Then, we focused on the possibility to develop asymmetric aza-Henry/ cyclization in the presence of readily available PTC or organocatalysts, as showed in the following table.



Scheme 3.2.4

entry	catalyst/base	*C* (M)	solvent	*T* (°C) step 1	time (h) step 1/step 2	yield (%)	ee
1	I/KOH	0.05	*m*-Xylene	–20	8/21		
2	I/K_2CO_3	0.05	*m*-Xylene	–20	24/48		
3	II/K_2CO_3	0,5	*m*-Xylene	–20	24/41	58	44
4	II/KOH	0.05	*m*-Xylene	–20	8/21		
5	II/K_2CO_3	0.1	*m*-Xylene	–20	27/45	83	76
6	II/K_2CO_3	0.1	toluene	–40	79/89	83	88
7	II/K_2CO_3	0.1	DCM	–40	38/48	68	72
8	II/K_2CO_3	0.2	toluene	–40	29/47	85	96
9	III/K_2CO_3	0.2	toluene	–40	50/90		
10	IV/K_2CO_3	0.2	toluene	–40	96/72	57	–72
11	V/K_2CO_3	0.2	toluene	–40	50/48		

Table 3.2.1



Even though in literature, PTC in combination with excess of strong base, was the best way to accomplish enantioselective addition of nitromethane to α-amidosulphones derived from aromatic aldehyde, in this case we didn't detect any cyclic product (**entries 1-4, table 3.2.1**). Carrying out the reaction under these conditions we observed only decomposition starting material, probably due to saponification of benzoates moiety.

Therefore, we focused our attention on a different catalytic system, employing thiourea bifunctional organocatalysts, the Takemoto's catalyst, in combination with weak inorganic base to promote in situ formation of imine.

In presence of K_2CO_3, the desired product was obtained carrying out the reaction at -20°C for the addition step, then cyclization was carried out increasing the temperature to r.t. (**entry 5**, **table 3.2.1**). Each step of the reaction could be followed easily by TLC analysis.

Nicely, we observed a significant improvement of selectivity increasing the $MeNO_2$ equivalents and the medium concentration and decreasing the temperature till -40°C in the addition step. This allowed to obtain 3-substituted isoindolinone with ee up to 96% (**entry 8, table 3.2.1**).

For comparison, we also carried out the reaction with other catalytic systems. For example, quinine catalyst III was not effective in the cyclization step (**entry 9, table 3.2.1**). The thiourea catalyst IV derived from epi-quinine, led to the formation of desired product in good yield and moderate ee (**entry 10, table 3.2.1**). This indicated that bifunctionality and hydrogen bond network are meaningful for the success of the process.

Some further control experiments were set up to investigate the trend of the reaction.

In particular, we investigated the synthesis of racemate performing the reaction with only use of weak inorganic bases such as K_2CO_3 or Cs_2CO_3 or organic base (Et_3N), in many different solvents as acetonitrile and toluene, at different temperature (room temperature or 50°C), leading to ineffective results.

In all the cases, it was clear that the cyclization was achieved with difficulty in low yields under the condition employed, and decomposition products were mainly observed. This trend showed that bifunctionality of thiourea catalyst is not only important for the addition step but also for the cyclization, probably due to the contemporary activation of the carbonyl moiety and deprotonation of the nitrogen promoted by the catalyst.

Proposed mechanism of cyclization

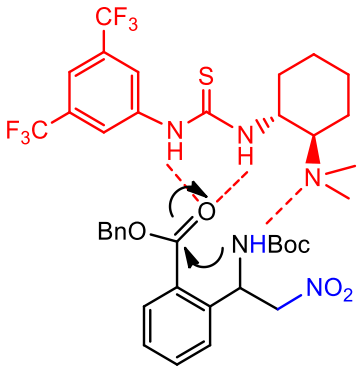
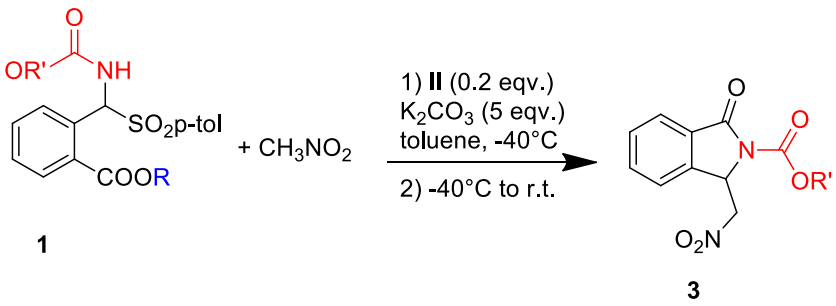


Figure 3.2.1

In fact, in the presence of Takemoto's catalyst, we were able to isolate the intermediate adduct to investigate the level of enantiopurity and we found out it showed the same level of enantiopurity as the cyclic product.



Scheme 3.2.5

entry	R	R’	time (h) step 1/step 2	yield (%)	ee
1	Bn	t-Bu	29/47	3a, 85	96
2	Bn	Bn	24/46	3b, 78	92
3	Me	t-Bu	32/48	3a, 56	76

Table 3.2.2

Then, we investigated how the protecting and the ester group influenced the selectivity of reaction.

N-Cbz amidosulphone led to N-Cbz isoindolinone in a good yield and high level of enantiopurity.

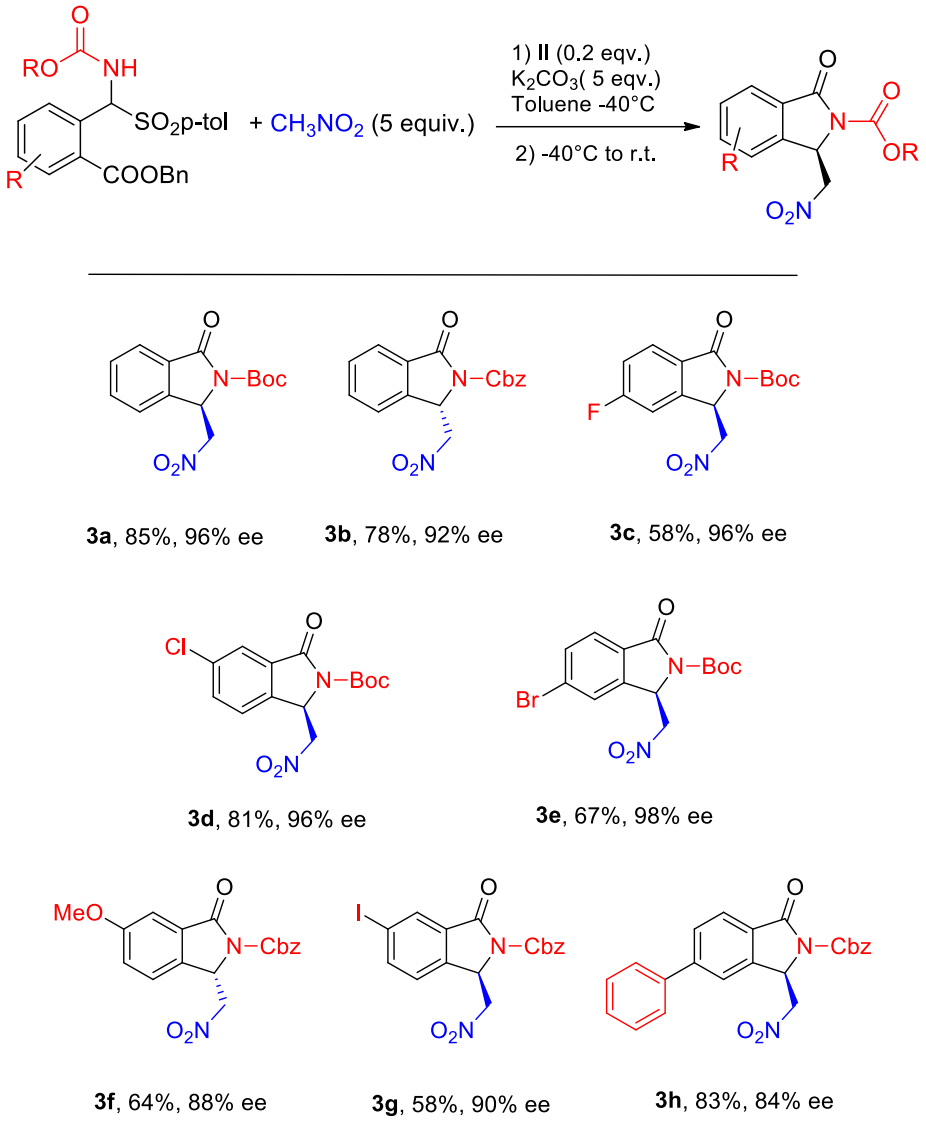
The ester group was found important in the selectivity of the process as well. In fact, methyl ester, as we can see in the entry 3 (**table 3.2.2**), was less effective than benzyl ester in terms of yield and enantioselectivity reported in entry 1. Furthermore, we can also observe the slightly increasing of reaction time in the reaction with methyl ester, probably because the methoxyl is a less effective leaving group than benzoxyl ester.

The scope of the method was investigated with novel α-amidosulphones with further substituents on aromatic rings, whose synthesis is reported in the experimental part of the thesis.

This was an interesting goal since N-tosylimines derived by 2-formylbenzoates were difficult to achieve with different substituents on the aromatic ring, in fact in the previous work this aspect wasn’t investigated.

This new class of enantioenriched compounds was obtained under the optimized conditions in moderate to high yield and with very high ee, in some case up to 98%. Different derivatives were synthetized with electron-withdrawing or -donating groups. We noticed that final ee is not related with the nature of the substituents on the aromatic ring.

In some cases, the presence of N-Cbz protecting group was necessary because analogues α-amidosulphones with N-Boc group were not stable and they were difficult to isolate. Also, with N-Cbz protecting group, very good results were obtained with enantioselectivities only slightly lower than N-Boc protected derivatives.



Scheme 3.2.6

As mentioned before, the racemates were achieved in low yield and only in some particular cases, so for the analytical determination of enantiopurity we compared chromatograms of the opposite enantiomers obtained in presence of the readily available ent-II, which also furnished reproducible results.

With X-ray analysis of single crystal of product **3e,** we determined the absolute configuration.

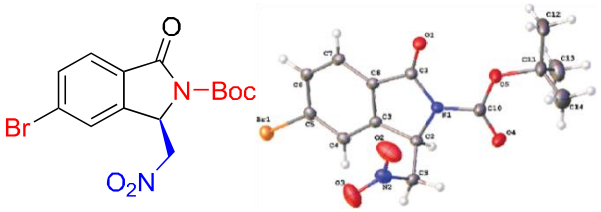
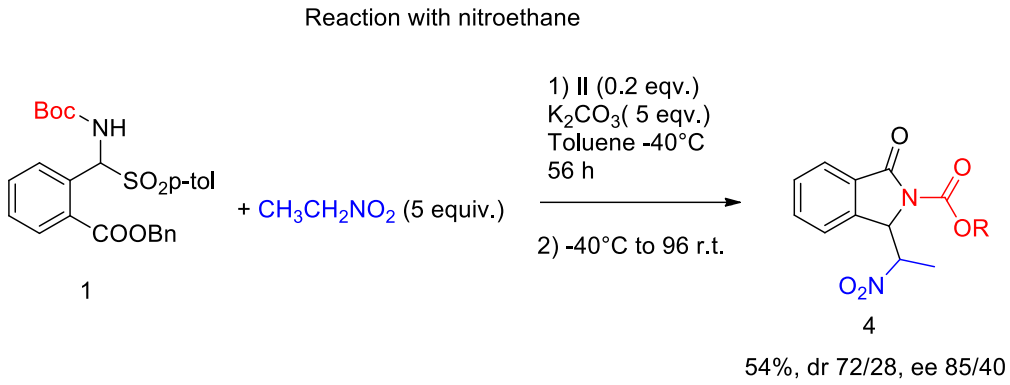


Figure 3.2.2

Several trials were conducted employing nitroethane as nucleophile, but the experiments were more difficult to handle because the formation of diastereomeric mixture. However, after longer reaction time we reached out the final product with good diasteroselectivity and good ee for the major diasteroisomer (85%).



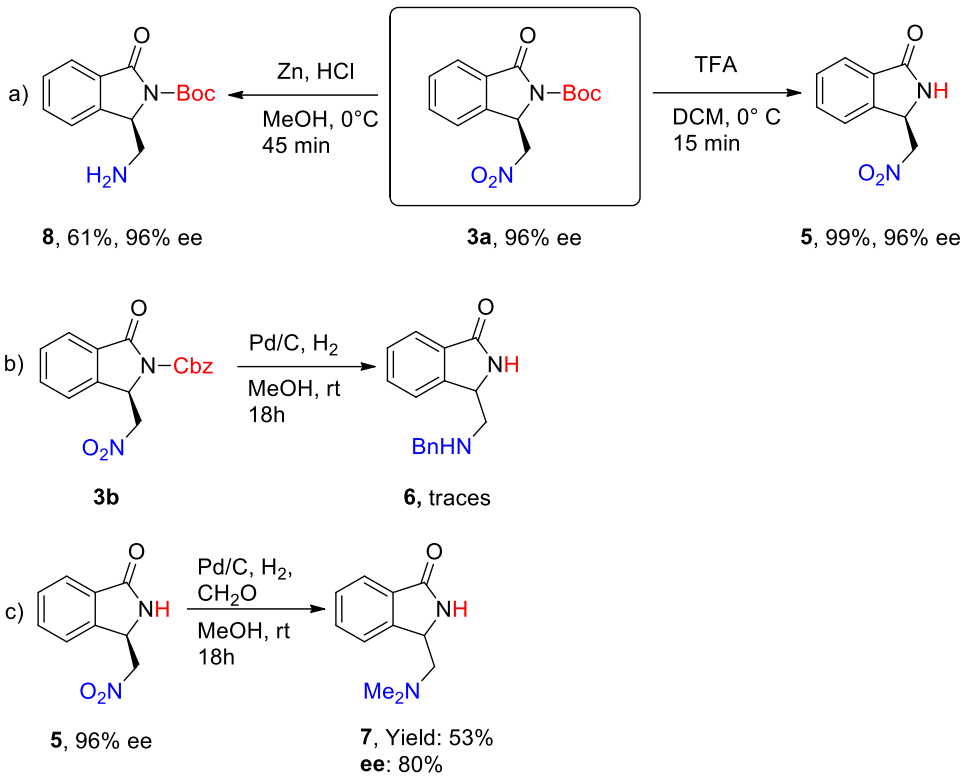
Scheme 3.2.7

In the end we investigated the second reactivity of these new compounds. Deprotection from the N-Boc group was achieved treating product **3a** with TFA in DCM at 0°C for 15 minutes, isolating the deprotected isoindolinone in quantitative yield without changes in terms of enantiopurity.

The reduction of nitro group required more efforts. First, we tried classical reduction employing H_2 and Pd/C employing as starting material the product **3b**, according to **Scheme 3.2.8**. However, results were not satisfying. We detected a complex mixture of products mostly due to side coupling reaction of benzyl group catalysed by Pd in those conditions.

Then, we tried to accomplish reduction of nitro group in another way, employing deprotected product under the same conditions, H_2 and Pd/C, according to **Scheme 3.2.8**. However, what we isolated was a mixture of products containing N,N-dimethylated amine. This is probably due to the presence of formaldehyde in traces that led to a reductive amination. Using these conditions, we detected a little loss of enantiopurity in the final product.

The disappointing results persuaded us to focus our efforts on some other reduction techniques. We decided to use Zn with a little amount of HCl in MeOH in the attempt to selectively reduce the product **3a** without affecting the N-Boc. Under these conditions we nicely obtained the new N-Boc protected 3-aminomethyl isoindolinone in good yield and unchanged enantiopurity.



Scheme 3.2.8

3.2.3 Conclusions

In conclusion we reported a new highly enantioselective process to achieve new 3-substituted isoindolinones with nitromethyl side chain in good yield and very high ee. The synthesis of substituted α-amidosulphones allowed an unprecedented route for asymmetric aza-Henry cascade reaction, and the use of Takemoto catalyst was found of essential importance not only for guarantee the high selectivity of process but also for permitting final lactamization of intermediate product. Boc-deprotection and the selective reduction of the nitro group were also carried out, leading to other novel isoindolinonic platforms in good yields and unchanged enantiomeric purity.

3.3 Synthesis of isoindolinones of pharmaceutical interest (Panzinaclone and PD172938 analogs)

In this section we report an efficient cascade reaction of 2-acetylbenzonitrile, promoted by K_2CO_3, in the total synthesis of biologically active isoindolinones, in particular of 3-methylated analogs of PD172938 and Pazinaclone[51].

We focused our attention on the organocatalytic synthesis of the intermediate that allowed the access to the key building block for the synthesis of 3-methylated analog of (S)-PD172938 with high enantioselectivity. This synthetic pathway can be of particular interest for medicinal chemistry because of the possibility to design and synthesize new and more effective bioactive compounds.

3.3.1 Background

The importance of methyl group influencing mechanism of action in many different pharmaceutical compounds attracted the attention of organic and pharmaceutical chemistry. In fact, more than 80% of small-molecule drugs contain at least one methyl group bound to a carbon atom. The introduction of methyl group is often linked to optimization of many pharmaceutical proprieties in drugs because of the so-called magic methyl effect.

This effect concerns to produce significant increasing of solubility and selectivity, and in some case in the conversion of an agonist to an antagonist or partial antagonist into a negative allosteric modulator.

In contrast with CF_3 group, which was an important topic of study for the synthetic community, the incorporation of methyl group is still a relevant challenge in many contexts, in particular when it needs to be inserted on an existing stereocenter.

Any synthetic protocols able to incorporate methyl group in a specific position are of high value to medicinal chemistry and pharmaceutical industry, especially for influence of methyl group in SAR (structure activity relationships) investigations.

Recently, isoindolinone scaffold has emerged as good pharmacophore showing a wide range of pharmaceutical activities such as antimicrobial, anti-Parkinson, antipsychotic anti-infiammatory etc. Some of these analogues reported in the following figure have interesting proprieties as dopamine D_4 ligand or benzodiazepine receptors agonist in the treatment of anxiety.

[51] A. Di Mola, G. Nicastro, L. Serusi, R. Filosa, M. Waser and A. Massa , *Molecules*, **2022**, 27, 5647

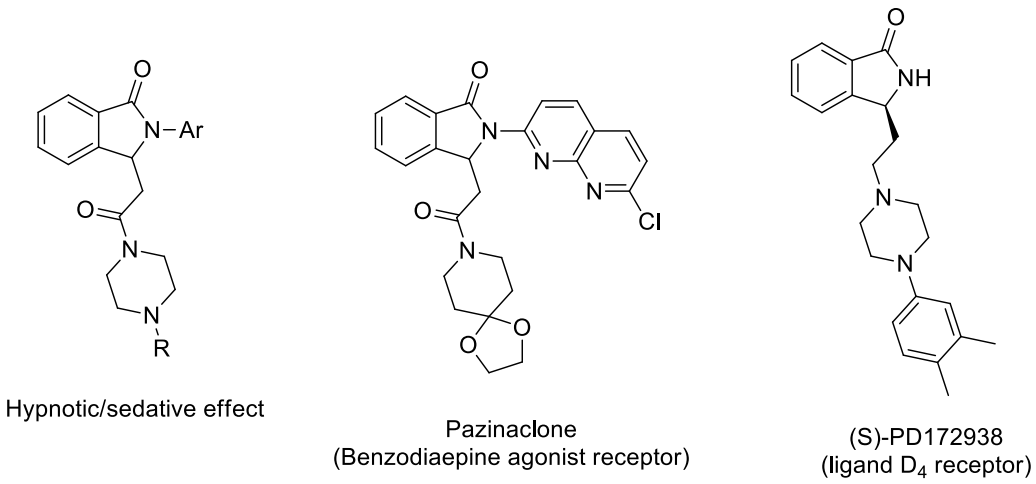
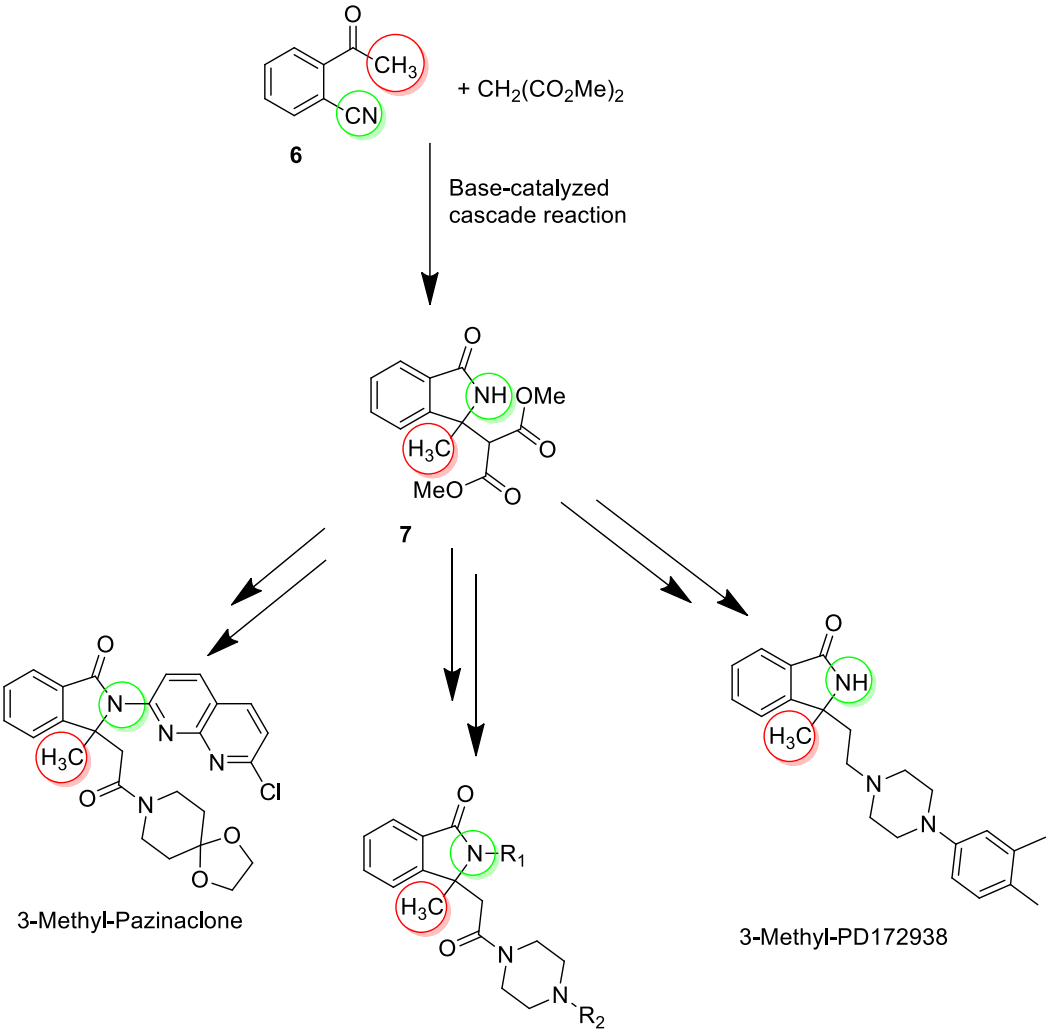


Figure 3.3.1

The incorporation of methyl group in the stereocenter can be of meaningful importance in binding and selectivity for receptors, and the construction of isoindolinone ring bearing a tetrasubstituted stereocenter could be particularly challenging, especially if we consider an asymmetric version of this synthesis.

Based on our continuing research interest in synthesis of this kind of molecules, we developed an efficient and useful synthetic protocol to afford 3-methylated analogues of Pazinaclone, PD172938 and other derivatives, through facile cascade reaction promoted by K_2CO_3. An efficient synthetic pathway to access 3-methylated analogue of (S)- PD172938 was also developed with asymmetric phase-transfer-catalysis process and sequential crystallization.



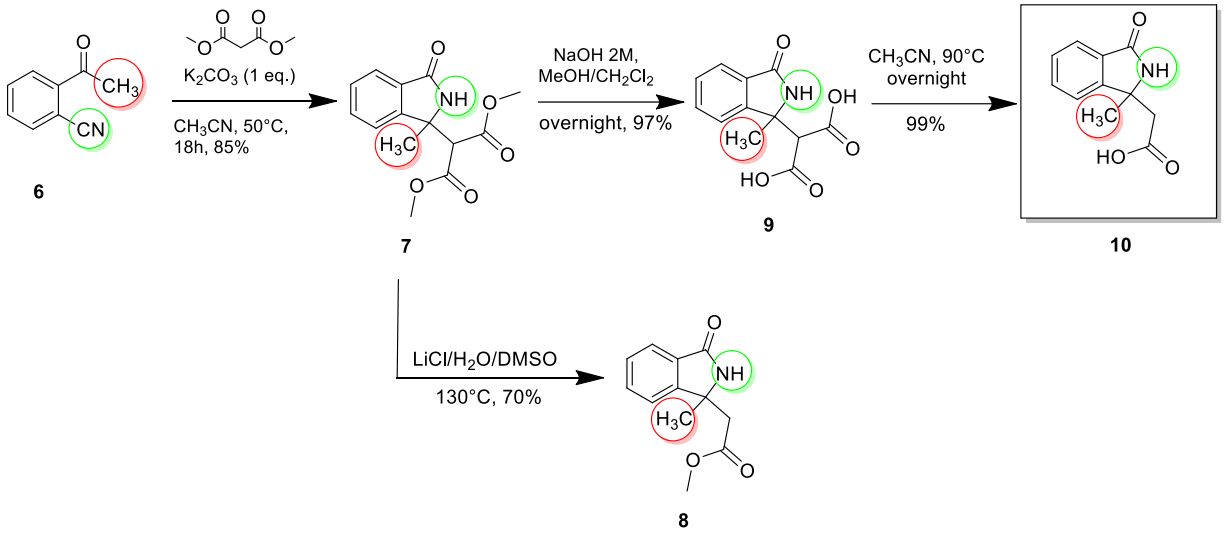
Scheme 3.3.1

3.3.2 Results and Discussion

The first part of our work concerns the large-scale synthesis of 3,3-disubstituted isoindolinone through a cascade reaction promoted by K_2CO_3, employing as starting materials 2-acetylbenzonitrile and dimethylmalonate in acetonitrile[52]. The obtained compound showed a very good versatility for synthesis of different bioactive analogues based on further manipulations to obtain monocarboxylic derivative.

The isoindolinone **7** can be decarboxylated through two different pathways: the procedure which employs HCl 6M at reflux and the other one with LiCl/H_2O/DMSO at 130°C also known as Krapcho decarboxylation. The first pathway led to a complex mixture of products; on the other hand, the second route furnished the product in good yield (70%). However, the monocarboxylated product can be easily obtained in very good yield by a two-step procedure from isoindolinone **7**: saponification with NaOH of the product **7** followed by mono decarboxylation under reflux in acetonitrile.

[52] G. Monaco, M. Tiffner, A. Di Mola, W. Herrebout, M. Waser, A. Massa, *Molecules* **2020**, *25*(10), 2272



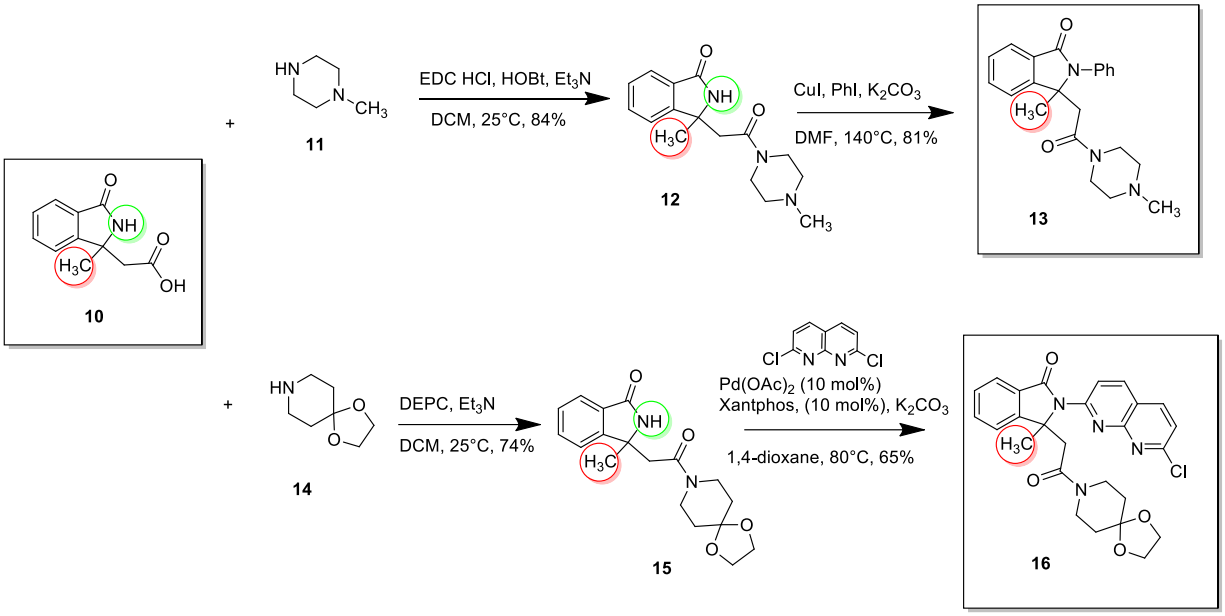
Scheme 3.3.2

The intermediate **10** was easily converted into the desired derivatives. Amide **12** derived from N-methylpiperazine **11** was easily achieved employing simple procedure with EDC/HOBt to activate the carboxylic group. Concerning the synthesis of 1-piperidone ketal **14**, Yamada coupling using DEPC was found more useful to reach out the target product[53].

NH-arylation of lactams **12** and **15** required more efforts. Despite arylation of 3-monosubstituted isoindolinones, phenylation of lactam **12** was carried out employing ligand-less cross coupling reaction based on the Cu(I)-catalyzed arylation of amides in a very good 81% of yield, allowing to afford 3-methylated analogue **13** of a hypnotic sedative drug. In synthesis of 3-methylated Pazinaclone **16**, the previous reaction catalyzed by Cu(I) were not effective to afford the desired derivative in a efficient pathway[54]. On the contrary, to carry out product **16** the palladium-catalyzed Buchwald–Hartwig reaction of the lactam **15** in the presence of Xantphos was necessary with the less reactive 1,8-dichloronaphthiridine.

[53] Yamada, S.I.; Kasai, Y.; Shioiri, T.S., *Tetrahedron Lett.*, **1973**, 14, 1595–1598

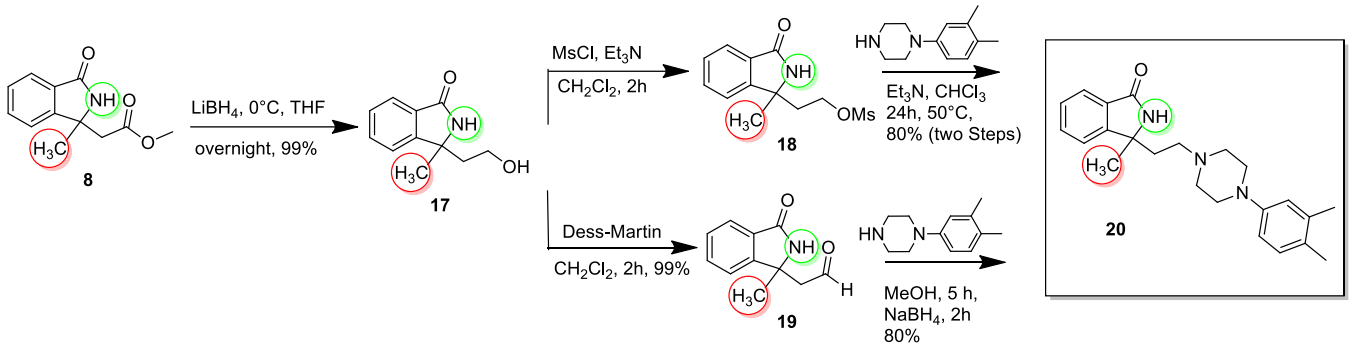
[54] Sughara, M.; Ukita, T., *Chem. Pharm. Bull.* **1997**, *45*, 719–721



Scheme 3.3.3

Concerning the compound **20**, the analogue methylated of PD172938 was obtained as follows.

First we proceeded with selective reduction of ester **8** with $LiBH_4$, affording the reduction product in quantitative yield. Afterwards, mesylation of alcohol **17** and displacement of mesyl group by 3,4-dimethylphenylpiperazine, led to methylated analogue of PD172938 **20** in high overall yield. About that we immediately noticed that one-pot reaction mesylation/piperazine displacement led to ineffective results. The best result was achieved using **18** as crude product, performing the reaction with 3,4-dimethylphenylpiperazine in $CHCl_3$ at 50°C. These conditions allowed to afford PD172938 **20** in 80% of yield for two consecutive steps. Alternative, synthesis of product **20** was easily accomplished with similar results via reductive amination of aldehyde **19** obtained by quantitative Dess-Martin oxidation of the alcohol **17**, while the reduction of **8** in **19** was not attempted since DIBAL-H is not selective in the presence of amides.



Scheme 3.3.4

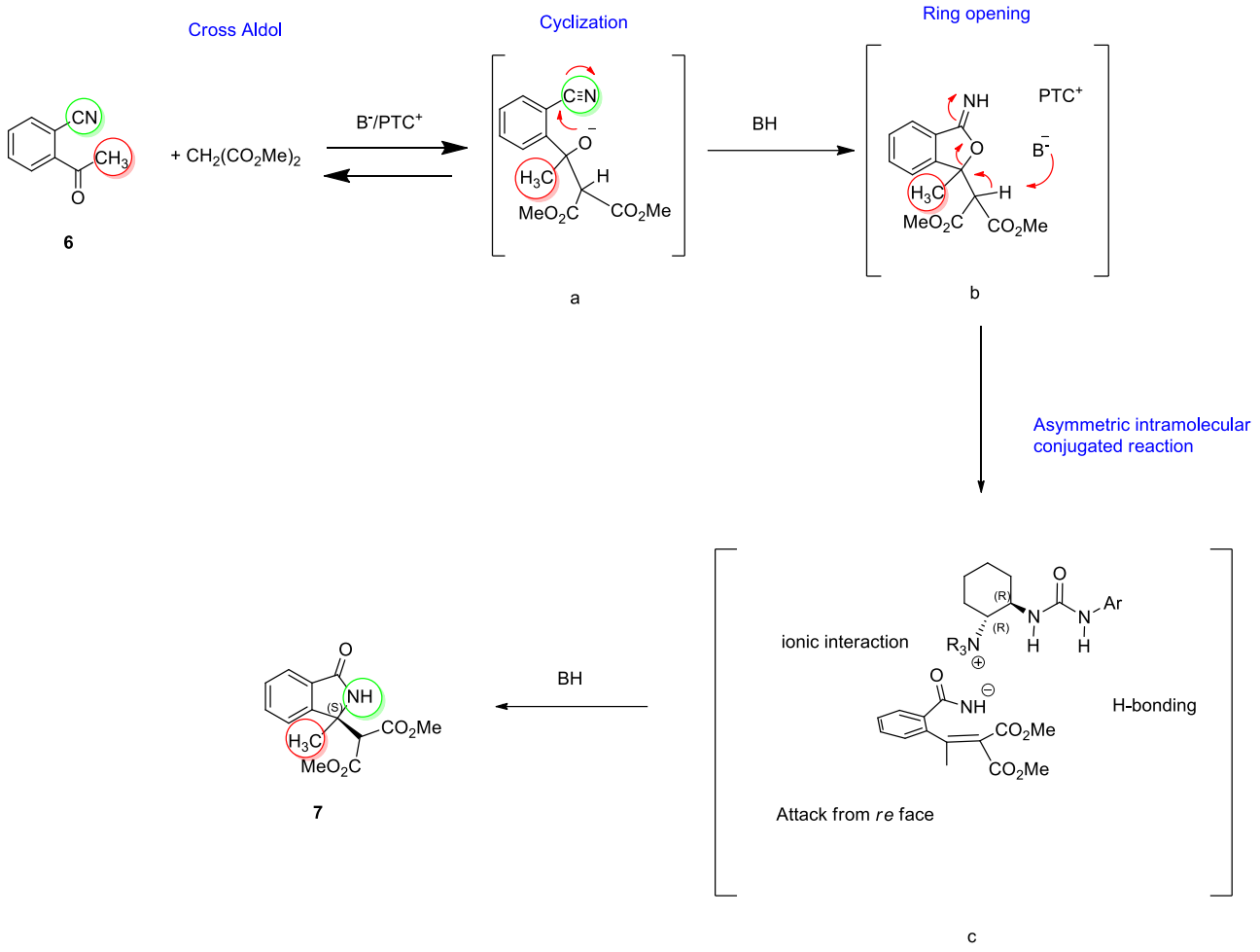
Then, asymmetric synthesis of (S)-PD172938 was investigated. For direct application in medicinal chemistry trials, the opportunity to construct a new stereocenter selectively is of great importance. Since the synthesis of the enantioenriched key intermediate **8** and related compounds bearing tetrasubstituted stereocenter has never been performed, we focused all efforts on asymmetric synthesis of compounds **7** through cascade reaction with 2-acetylbenzonitrile and dimethylmalonate.

As demonstrated in a preliminary report, the development of such a strategy was particularly challenging. A large number of chiral neutral bifunctional organocatalysts and chiral ammonium salts were employed under different conditions[55]. The best results were achieved in the presence of the chiral bifunctional ammonium salt **21**-derived form (*R*,*R*)-1,2-cyclohexanediamine and K_2CO_3 as the inorganic base in CH_2Cl_2 under phase transfer conditions as described in the **scheme 3.3.5**.

The chance to easily synthetize the bifunctional catalyst allowed to scale-up the cascade reaction employing 1.72 mmol of 2-acetylbenzonitrile. Despite the moderate selectivity achieved also on large scale reaction, the ee of the product **7** was easily increased by crystallization up to 94% ee in acceptable overall yield. In addition, the catalyst was recovered after purification in 75% of yield and reused for the same reaction with comparable results, increasing the efficiency of entire process.

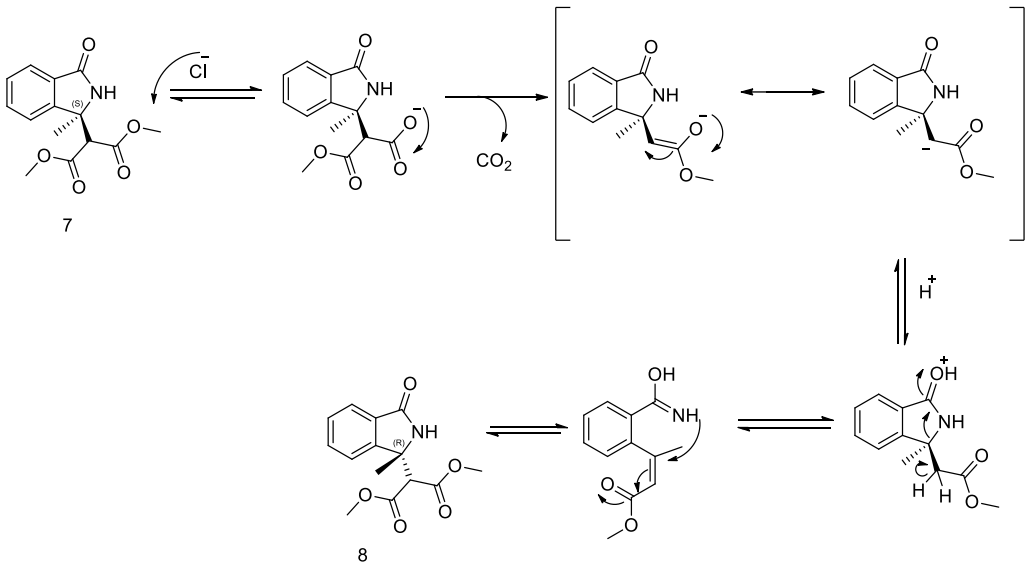
In the present investigation, we used (*R*,*R*)-**21** because as previously demonstrated it lead to **7** with (S) configuration[44]. The determination of absolute configuration was meaningful to hypothesize a plausible transition state for the enantioselective determining step. A combination of both ionic and hydrogen bond interactions with **21** should favour the intramolecular aza-Michael reaction from the *re* face of prochiral intermediate **c** leading to **7**. After deprotonation of dimethylmalonate, the resulting carbanion leads to carbonyl addition to ketone, followed by cyclization at cyano group and formation of the cyclic imidate **b**, which give then rearrangement to the final product **7**.

[55] G. Monaco, M. Tifner, A. Di Mola, W. Herrebout, M. Waser, and A. Massa, *Molecules* **2020**, 25(10), 2272-2278



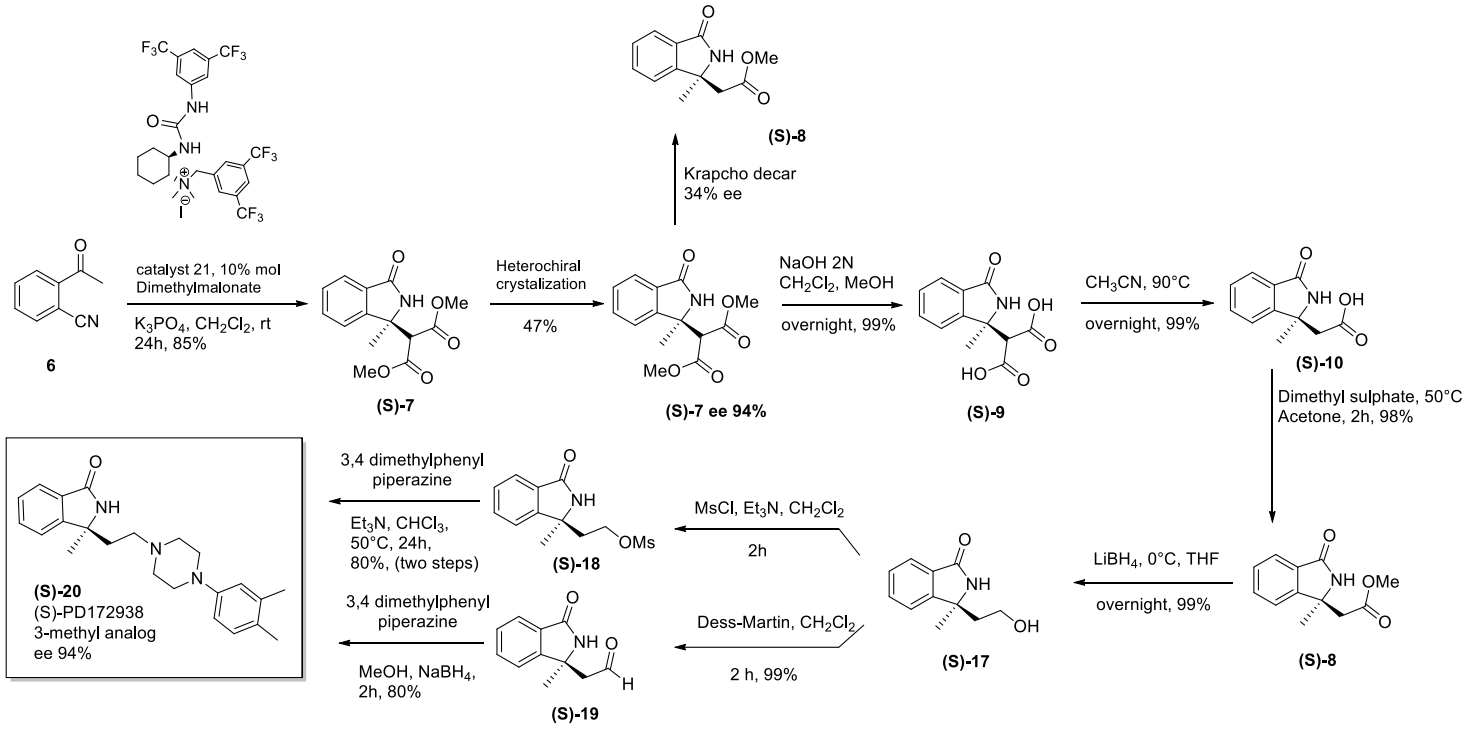
Scheme 3.3.5

The synthesis of (S)-**10** was successively carried out through two step decarboxylation affording the product in unchanged enantiopurity. Few attempts have been done following Krapcho synthesis because product **7** can be turned into monoester **8.** However, product **8** was recovered observing a significant racemization probably due to reversible opening/ring closing via retro-Michael reaction promoted by high temperature.



Scheme 3.3.6

The final compound (S)-**20**, 3-methylated analog of (S)-PD172938, was obtained by the two different synthetic strategies as previously mentioned for racemate synthesis: via the mesyl group displacement in (S)-**18** or reductive amination of aldehyde (S)-**19**, without loss of enantiopurity in both the cases (94% ee) and good overall yields.



Scheme 3.3.7

3.3.3 Conclusions

We reported the first racemic procedure to access of 3-methylated analogs of valuable biologically active isoindolinones with tetrasusbstituted stereocenter. In particular, 3-methyl-Pazinaclone was achieved in five steps and 39% overall yield. 3-Methyl-PD172938 was obtained in seven steps and about 60% overall yield. Since the (S) enantiomer of PD172938 has been reported to show superior biological activity, asymmetric synthesis of its 3-methylated analog was also developed based on asymmetric phase transfer catalysis cascade process. The final product was obtained with high enantiopurity (94% ee) in eight steps and about 30% overall yield.

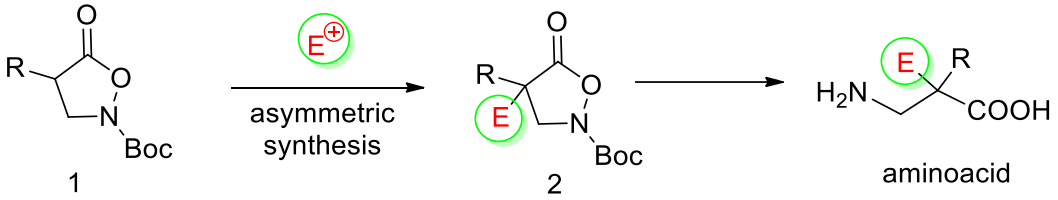
3.4 Phthalides hybrid compounds

In this paragraph we report the protocol for the asymmetric aldol-initiated cascade reaction of nucleophilic isoxazolidin-5-ones to ortho-cyanobenzaldehydes, suitable building block in the synthesis of phthalides scaffold, using Takemoto's bifunctional organocatalyst[56]. This novel synthetic approach allows facile access to various interesting hybrid heterocyclic compounds which were then transformed into $\beta^{2,2}$-amino acid-phthalide with good enantio- and diastereoselectivities in reasonable yields. Further investigation about ring-opening of these compounds to acyclic carboxylic acid derivatives has been reported too.

3.4.1 Background

In these years isoxazolidin-5-ones emerged as potential masked $\beta^{2,2}$-amino acids analogues[57-58]. The most important value of this class of compounds relies in the fact they can be easily used for a variety of asymmetric α-functionalization reactions for delivering $\beta^{2,2}$-amino acids derivatives straightforwardly[59-60]. So far, this strategy has been found very effective for application to asymmetric heterofunctionalizations, as well as C-C bond-forming processes, employing chiral organocatalysts but also with different catalytic strategies such as transition metal catalysis[61-62].

In addition, the highly functionalization of the chiral compounds with opening ring of isoxazolidin-5-ones, was found as very facile access for reach out free amino acids and peptides, as demonstrated in recent publications.

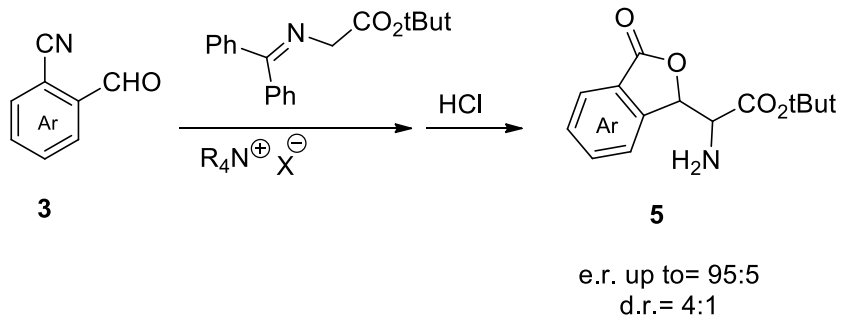


Scheme 3.4.1

Another class of interesting compounds is 3H-isobenzofuran-1-ones, or phthalides. A few years ago, our research group, in collaboration with prof. Waser from University of Linz, developed a novel cascade reaction promoted by a chiral bifunctional ammonium salt between 2-cyanobenzaldehyde and glycine's

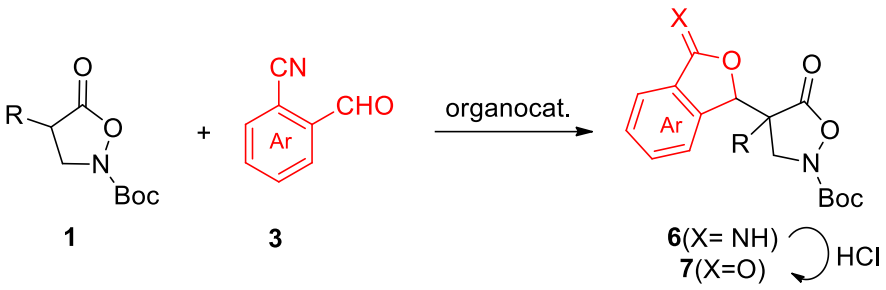
[56] L. Serusi, P. Zebrowski, J. Schörgenhumer, A. Massa, and M. Waser; *Helvetica Chimica Acta*, **2022**
[57] J. Annibaletto, S. Oudeyer, V. Levacher, J.-F. Brière, *Synthesis,* **2017**, 49, 2117–2128.
[58] H. Noda, M. Shibasaki, *Eur. J. Org. Chem*., **2020**, 2350–2361
[59] T. Tite, M. Sabbah, V. Levacher, J.-F. Brière, *Chem. Commun*. **2013**, *49*, 11569-11571.
[60] V. Haider, P. Zebrowski, J. Michalke, U. Monkowius, M. Waser, *Org.Biomol. Chem.* **2022**, *20*, 824-830
[61] J.-S. Yu, H. Noda, M. Shibasaki, *Angew. Chem. Int. Ed*. **2018**, *57*, 818–822
[62] A. Eitzinger, M. Winter, J. Schörgenhumer, M. Waser,*Chem. Commun*. **2020**, *56*, 579-582

Schiff base leading to an easy access to the α-amino acid-phthalide hybrids, upon acidic hydrolysis of the primarily formed imidate species as well as the ketimine group[63-64].



Scheme 3.4.2

Considering the potential of 2-cyanobenzaldehyde, we investigated the asymmetric addition of isoxazolidin-5-ones to this aldehyde under organocatalytic conditions, to access new phthalidic hybrids. This strategy will give access to a series of highly functionalized compounds **7** (upon acidic hydrolysis of the initial reaction products **6,** and will thus provide a straightforward entry to novel β[2,2]-amino acid-phthalide conjugates.



Scheme 3.4.3

[63] M. Perillo, A. Di Mola, R. Filosa, L. Palombi, A. Massa, *RSC Adv.*, **2014**, *4*, 4239–4246.

[64] A. Di Mola, F. Scorzelli, G. Monaco, L. Palombi, A. Massa, *RSC Adv.*, **2016**, *6*, 60780–60786.

3.4.2 Results and Discussion

Based on our previous experiences of asymmetric reactions of 2-cyanobenzaldehyde **3,** we tested some easily available chiral ammonium salts and organobases to find the best conditions for our target reaction[65-66-67].

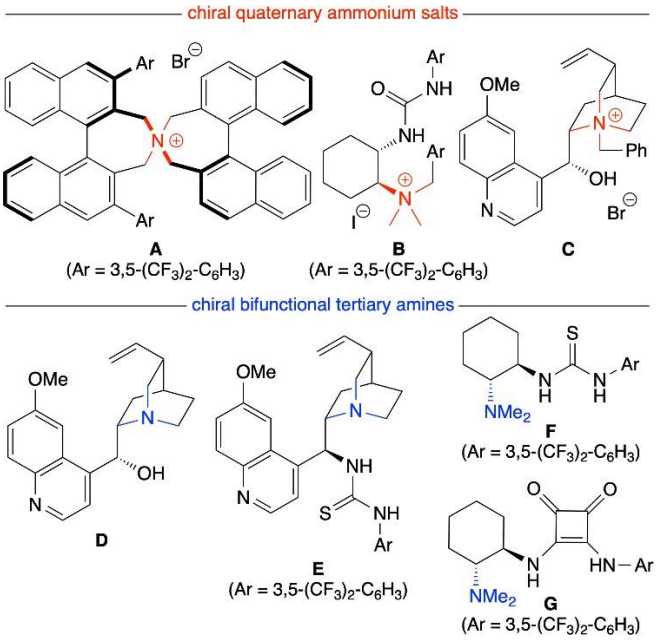


Figure 3.4.1

We started our investigation finding the best reaction conditions. In particular we optimized the enantioselective addition of isoxazolidin-5-ones **1a** to 2-cyanobenzaldehyde. The uncatalyzed reaction performed good with the only presence of K_2CO_3 as base, affording the product **7a** as a mixture of diasteroisomers, after acidic hydrolysis of the intermediate **6a**.

The first attempt to get the final product with enantioselective approach was carried out the reaction using chiral ammonium salts **A-C**, which we used in previous reactions with pronucleophile **1** as well as acceptor **3**.

Unfortunately, it was not possible to achieve reasonable levels of enantioselectivity, and for these unexpected results we decided to overcome screening the bifunctional catalysts **D-G**.

The Cinchona alkaloid quinine **d** was used in the reaction with and without external base, and here we observed the first increasing of enantioselectivity in the final product, but unfortunately the outcome could not be improved further by using other Cinchona alkaloid derivatives or changing the conditions. Then, we

[65] V. Capaccio, K. Zielke, A. Eitzinger, A. Massa, L. Palombi, K. Faust, M. Waser, *Org. Chem. Front*. **2018**, *5*, 3336-3340.

[66] A. Eitzinger, M. Winter, J. Schörgenhumer, M. Waser, *Chem. Commun*. **2020**, *56*, 579-582.

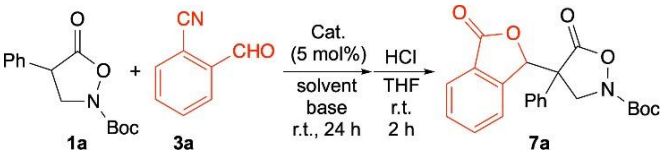
[67] A. Eitzinger, J.-F. Brière, D. Cahard, M. Waser, *Org. Biomol. Chem*. **2020**, *18*, 405-408.

did another attempt employing the thiourea catalyst **E**, which demonstrated the beneficial effects of thioureidic group for increasing the ee of final product.

After the attempts with Cinchona Alkaloid catalysts, we moved on screening Takemoto thioureidic catalyst. This allowed to find out the best condition to carry on the reaction. We achieved the best enantioselectivity (e.r. = 87:13 for the major diastereomer) combined with a reasonable isolated yield of 51% after 24 h reaction time.

Altough we noticed that unreacted starting material was still in the reaction mixture, longer reaction time didn't result to be useful for increasing yield in the final product, this was probably due to decomposition of the key intermediate in the reaction mixture.

In order to achieve a better isolated yield, the stoichiometric ratio of the two reaction partners was investigated and it was found that an excess of **1a** allowed for better yields compared to an excess of acceptor **3a**, and gladly we found out a little increase of selectivity of final target molecule. With this information in hand, we also tested the squaramide analog **G**, but unfortunately this catalyst was found to be less effective than the thiourea derivative. We therefore carried out the final optimization with Takemoto's catalyst **F**, but, as summarized in the following table, neither changing the solvent, nor lowering the temperature, or working under more diluted conditions allowed for any improvement anymore.



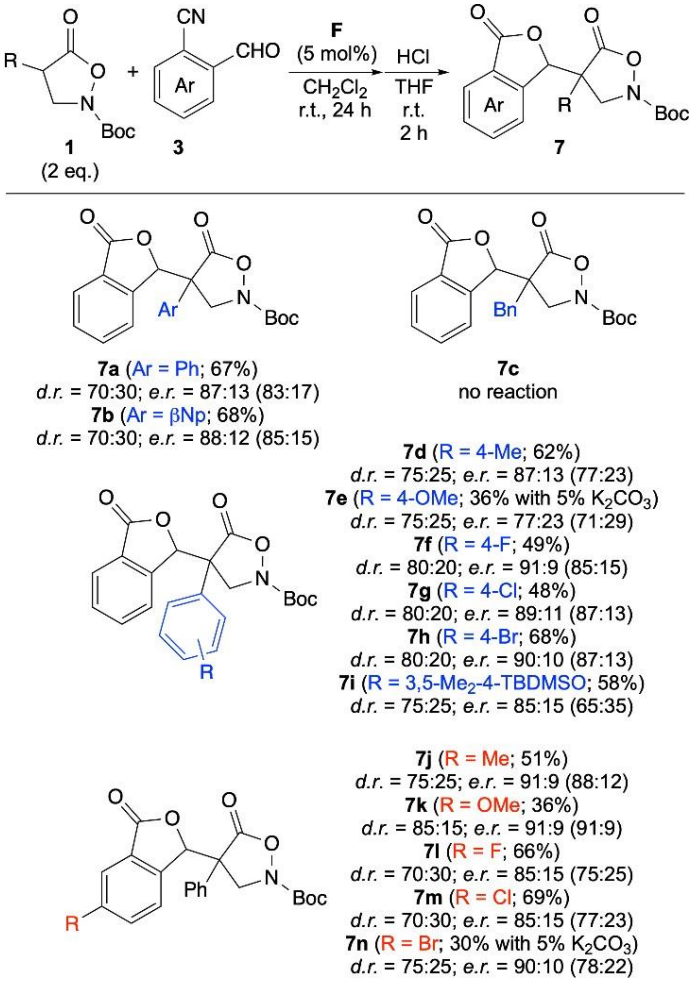
Entry[a]	Cat.	1a:3a	Solv.	Base	Yield [%][b]	d.r.[c]	e.r.[d,e]
1	-	1:1	CH_2Cl_2	K_2CO_3 (1 eq.)	67	65:35	-
2	**A**	1:1	CH_2Cl_2	K_2CO_3 (1 eq.)	44	80:20	rac.
3	**B**	1:1	CH_2Cl_2	K_2CO_3 (1 eq.)	59	65:35	rac.
4	**C**	1:1	CH_2Cl_2	K_2CO_3 (1 eq.)	26	85:15	55:45 (70:30)
5	**D**	1:1	CH_2Cl_2	K_2CO_3 (1 eq.)	38	60:40	57:43 (50:50)
6	**D**	1:1	CH_2Cl_2	-	54	70:30	75:25 (72:28)
7	**E**	1:1	CH_2Cl_2	-	18	90:10	78:22

							(77:23)
8	**F**	1:1	CH_2Cl_2	-	51	70:30	87:13
							(77:23)
9	**F**	1:2	CH_2Cl_2	-	27	80:20	89:11
							(77:23)
10	**F**	2:1	**CH_2Cl_2**	-	**67**	**70:30**	**87:13**
							(83:17)
11	**G**	2:1	CH_2Cl_2	-	31	65:35	76:24
							(69:31)
12	**F**	2:1	THF	-	36	70:30	80:20
							(79:21)
13	**F**	2:1	toluene	-	51	65:35	68:32
							(80:20)
14	**F**	2:1	CH_2Cl_2(0 °C)	-	59	70:30	85:15
							(75:25)
15	**F**	2:1	CH_2Cl_2 (-20 °C)	-	59	70:30	85:15
							(77:23)
16	**F**	2:1	CH_2Cl_2 (0.03 M)	-	34	75:25	81:19
							(80:20)

Table 3.4.1

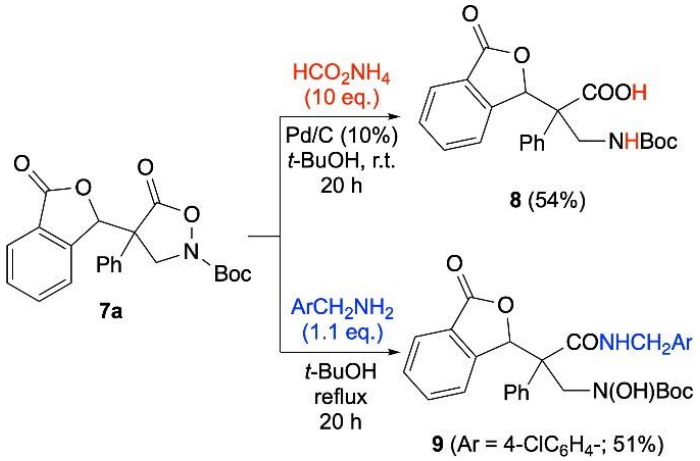
Then, we investigated the scope of the method for different substituted isoxazolidin-5-ones as showed in the next table.

Unfortunately, we discovered that this cascade reaction has some limitations. This reaction performed well only with α-aryl substituted isoxazolidin-5-ones. In fact, the analogous α-benzyl derivative was found to be unreactive and did not allow to the formation of product **7c**. On the other hand, a wide range of α-aryl groups were good tolerated, affording the product **7a,b,d,i** with reasonable selectivity. We also observed that conversion of some starting materials was incomplete after 24 h reaction time and especially in the presence of a strongly electron donating aryl group, as shown for product **7e**, led to significantly reduced reactivities. In fact, for the product **7e,** it was necessary to add catalytic amount of external base to achieve the formation of desired product, although the yield was still limited at 36%. Variations of the acceptor **3** were possible as well, as demonstrated for the successful formation of products **7j-n**, although here as well conversion of some starting materials was somewhat limited as we can see for the product **7n**, showing that some structural limitations exist.



Scheme 3.4.4

After investigation of the scope of the asymmetric cascade reaction between compounds **1** and **3**, we finally worked on the (reductive) ring-opening of compounds **7**. As outlined in the following scheme, the reductive N-O-cleavage could be carried out employing ammonium formate under Pd-catalysis, giving the free acid **8**. On the other hand, nucleophilic ring-opening was possible by addition of benzylamine derivatives, giving the amide **9** straightforwardly.



Scheme 3.4.5

Unfortunately, we have not been able to obtain any suited crystals of products **7** or of products **8** and **9** derived from ring opening to determine the relative or the the absolute configuration of these compounds by single crystal X-ray analysis. To get at least a plausible hint for the relative configuration of the products, then DFT calculations on compound **7a** were performed. Structure optimization revealed the unlike-configuration being slightly more stable than the like-isomer. For the geometries lowest in energy, ^{13}C-NMR shifts were computed using different methods and then compared to the experimentally obtained values for both.

3.4.3 Conclusions

We succeeded in developing a new synthetic pathway for the asymmetric cascade addition of isoxazolidin-5-ones **1** to ortho-cyanobenzaldehydes **3** by using Takemoto's bifunctional catalyst **F**. This novel approach allows for the synthesis of the novel β^{2,2}-amino acid-phthalide hybrids **7** with good enantio and diastereoselectivities and moderate yields after acidic hydrolysis of the primary reaction products **6**. The attitude of these compounds to undergo further ring-opening reactions was also demonstrated, giving access to the acyclic β-AA derivatives **8** and **9**.

3.5 3-Isoquinolinones

In this last paragraph, we report a new cascade process for easy access to 1-substituted isoquinolinones. In particular, an environmentally friendly Mannich initiated cascade reaction led to a new class of 1-substituted 3-isoquinolinones under catalyst free and solvent free conditions, in the presence of nitromethane and dimethylmalonate as nucleophile[68]. Further investigation about second reactivity of side chain in 1 position, showed the versatility of these class of molecules for meaningful manipulations in other synthetic pathways in which they could be involved.

3.5.1 Background

One of the main paradigms to pursuit efficient cascade type reactions in the synthesis of new heterocyclic compounds, is certainly the design of suitable starting materials bearing in their structure a proper combination of functional groups. As we saw previously, our group developed different and versatile cascade and multicomponent reactions for the easy access to many important heterocyclic scaffolds such as isoindolinones. As described in the previous paragraphs, nucleophilic addition to imines and α-amidosulphones derived from 2-formylbenzonitriles, has been found a good strategy to trigger cascade reaction useful in construction of the γ-lactam ring of different substituted isoindolinones.

In this work we focused our attention on the homologous building block 2-formylphenyl acetate with the final purpose to achieve the construction of the δ-lactam ring of diversified 3-isoquinolinones.

3-Isoquinolinones (1,4-dihydro-3(2H)-isoquinolinones, also named isoquinolin-3-ones), are important δ-lactams in field of organic and medicinal chemistry, showing a wide range of biologically activities. This class of compounds is suitable for further easy transformations into related heterocycles to give for example tetrahydroisoquinolines, a moiety found in many bioactive alkaloid analogs and natural products, as showed in the following example.

[68] L. Serusi, A. Di Mola and A. Massa, *RSC Adv*., **2023**, 13, 6557.

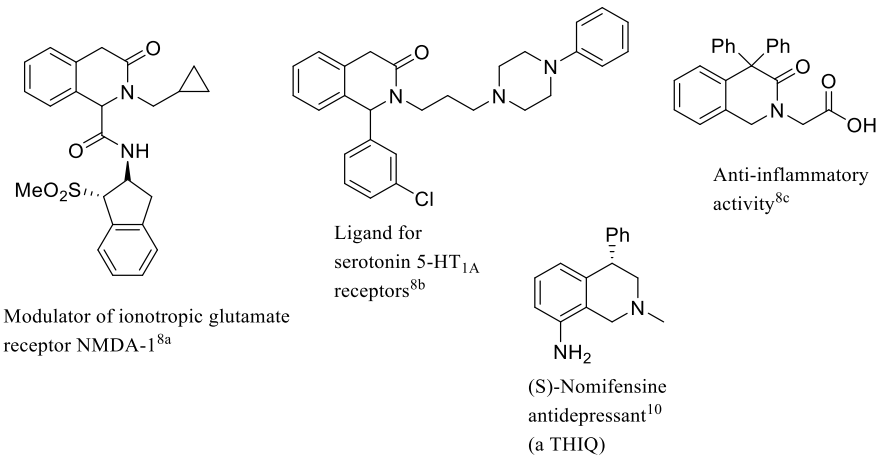
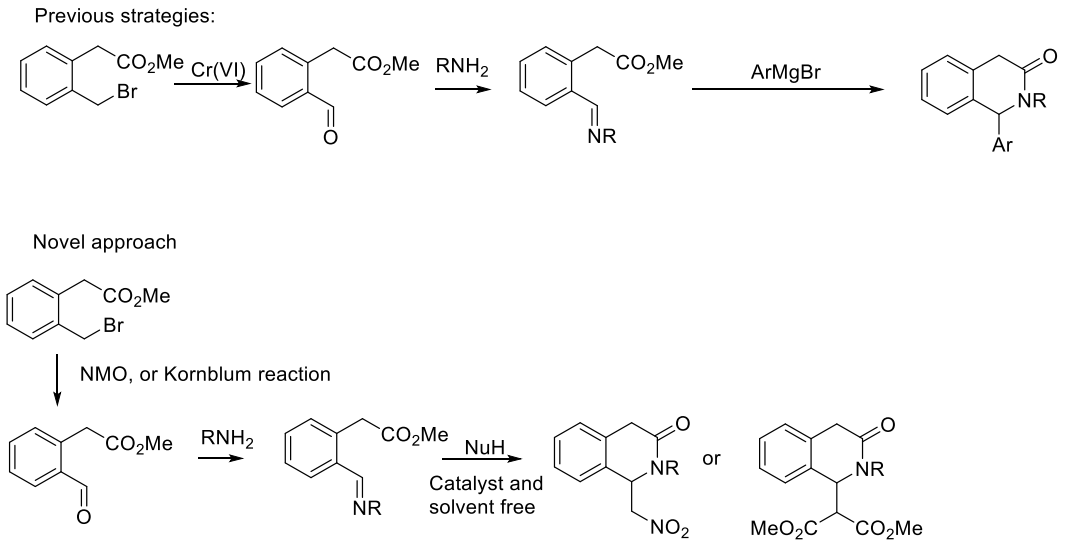


Figure 3.5.1

The introduction of different substituents in 1 position of 3-isoquinolinone ring is an important goal for the obtaining of substituted THIQs as well. For this purpose, a few methodologies are reported in literature, which mostly involves the addition of organometallic reagents to the imine derived from 2-formylphenyl acetate, followed by in situ lactamization[69]. Reductive amination/cyclization is a suitable pathway to achieve C-unsubstituted 3-isoquinolinones [70]. Other strategies to achieve this class of molecules are mainly limited to the reaction of isochroman-3-one with aromatic imines under very harsh reaction conditions under presence of transition metal catalysts at high temperature[71-72].



Scheme 3.5.1

[69] Wen Zhou, Yan-Xue Zhang, Xiao-Di Nie, Chang-Mei Si, Xun Sun, and Bang-Guo Wei, *J. Org. Chem.* **2018**, 83, 17, 9879–9889

[70] M. J. O' Sullivan a, R. J.D. Hatley, C. R. Wellaway, S. P. Bew, C. J. Richards, *Tetrahedron*, **2021**, 100, 132455

[71] Shvo, E.C. Taylor, K. Mislow, M. Raban, *J. Am. Chem. Soc.* **1967**, *89*, 4910-4917

[72]) K. Kim, S.H. Hong, *J. Org. Chem.* **2015**, *80*, 4152-4156

With this background in our mind, we thought that the use of these imines has been underestimated. The use of weak nucleophiles could allow the development of new cascade reactions for the facile access to new kind of 3-isoquinolinones. Surprisingly, this strategy wasn't explored before.

3.5.2 Result and Discussion

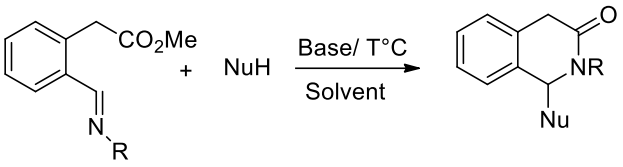
2-Formylphenyl acetate can be easily obtained by oxidation of the bromide derivative performed with Cr(VI) reagent. Because of the toxicity of this reagent, the route to achieve aldehyde was replaced by easy oxidation via Kornblum[73] reaction or oxidation with NMO (N-methyl morpholine N-oxide) (**scheme 3.5.1**). Even if the conversion was quantitative for both of experimental procedures, we preferred to perform the scale up, employing the NMO oxidation in order to avoid the use of DMSO and a more difficult work-up procedure. Then, the aldehyde was converted into imine derivative and employed in reaction with nucleophiles without any further purification, as crude starting materials.

For instance, reactivity of imines was investigated using carbon nucleophiles as nitromethane aiming to cascade process starting from an aza-Mannich reaction. To find the most useful reaction conditions, we firstly tested standardized base-promoted reaction condition in acetonitrile for the generation of nitronate anion. Even if we found out this method very helpful to trigger cascade reaction for synthesis of isoindolinones and isoquinolintriones, we noticed the procedure was totally ineffective to reach out our target product. Therefore, we considered a recent method of aza-Mannich reaction developed under catalyst-free conditions without any solvent but a slight excess of the nitromethane[74]. Attracted by this green approach, we quickly discovered the effectiveness of this novel strategy affording the target product, 1-nitromethyl-2-benzyl isoquinolin-3-one, in very high yield. Since the actual nucleophilic species is the nitronate anion, the imine should be enough basic to deprotonate nitromethane and promote addition of nucleophilic species. This proton exchange will increase the electrophilicity of the imine as well. Therefore, readily available pronucleophiles belonging to the class of double activated methylene compounds like dimethylmalonate (pKa=15.9), acetylacetone (pKa=13.3) and malononitrile (pKa=11.0) were investigated. The less acidic ketone acetophenone (pKa=24.7) was also tested for comparison. Malononitrile led to a complex mixture of products. Acetylacetone gave the expected isoquinolin-3-one only in traces and the side product, isochromanone, probably due to partial hydrolysis of the imine to respective aldehyde in the reaction mixture. DMM gave the heterocycle in good yield. On the other hand, in the presence of acetophenone we

[73] N. Kornblum, J. W. Powers, G. J. Anderson, W. J. Jones, H. O. Larson, O. Lbvand, W. M. Weaver *J. Am. Chem. Soc.* **1957**, *79*, 6562

[74] A. Pelagalli, L. Pellacani, E. Scandozza, S. Fioravanti *Molecules* **2016**, *21*, 723

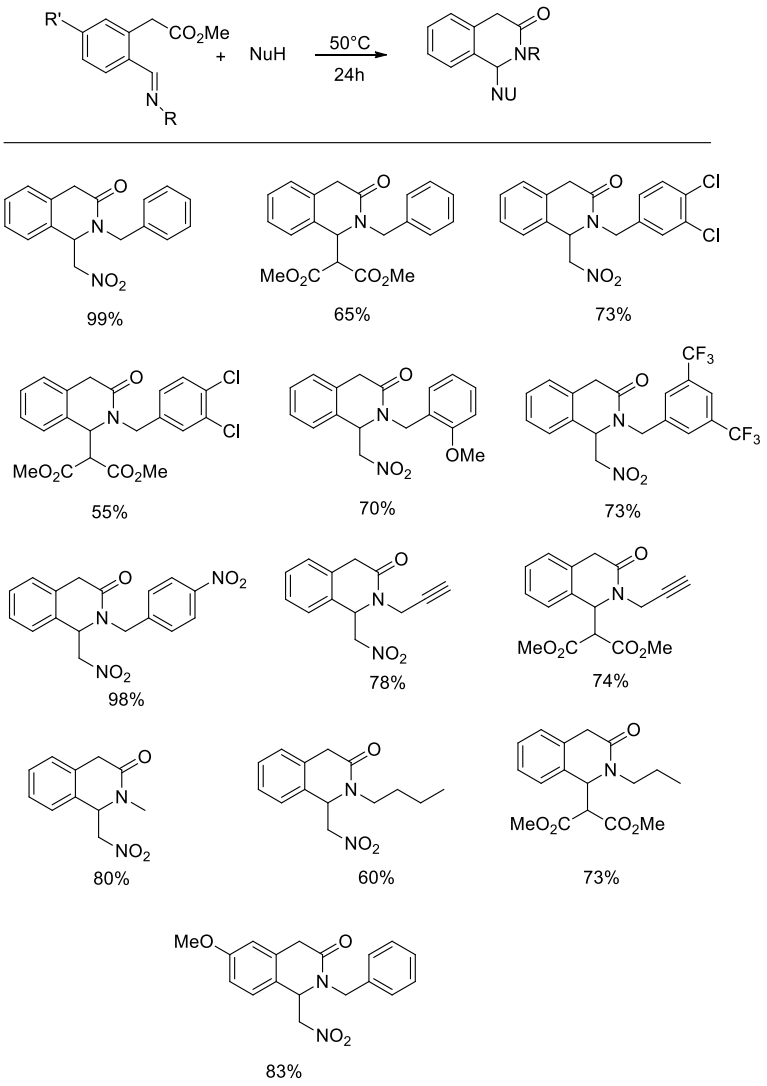
recovered the starting materials unreacted. The main results have been reported in the following table for optimization of reaction conditions.



Entry	Nucleophile	Base (1 eqv.)	Time (h)	T (C°)	Solvent	Yield (%)
1	CH_3NO_2	K_2CO_3	96	rt	CH_3CN	--
2	CH_3NO_2	-	18	50°	-	80
3	CH_3NO_2	-	20	50°	-	99
4	Dimethylmalonate	-	17	50°	-	65
5	Malononitrile	-	17	50°	-	Complex mixture
6	Acetylacetone	-	24	50°	-	Complex mixture
7	Acetophenone	-	24	50°	-	No reaction

Table 3.5.1

Then, the scope of the reaction was briefly analyzed using nitromethane and DMM in the presence of different N-benzylimines and N-alkylimines. In most cases we obtained the expected new products from good to high yields, irrespective of the presence of both electron-donating and electron-withdrawing groups on the benzylamine part of the substrates. Only the N-α-methyl benzylimine did not react probably because of the increased steric hindrance and aniline was not tested because the synthesis of the respective imine was sluggish.

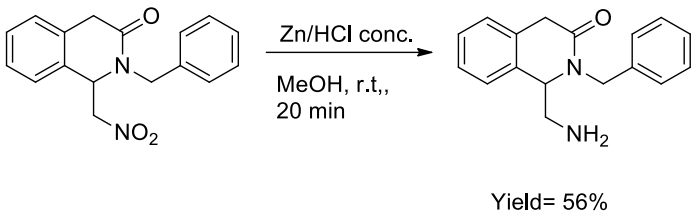


Scheme 3.5.2

After reaction scope, we investigated the second reactivity of both the final products obtained with nitromethane and DMM, to explore the versatility of this new class of compounds and extend their use in total synthesis of potential biologically active derivatives.

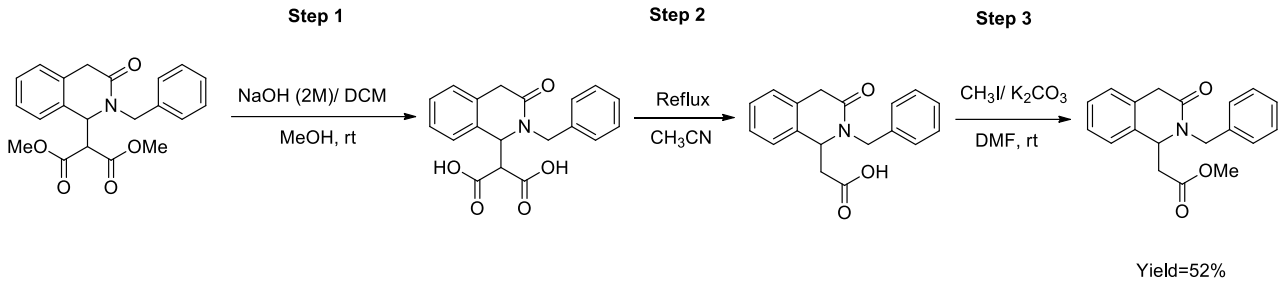
At first, we investigated the reduction of nitro group in order to achieve primary amine in the side chain. For this purpose, we followed the same strategy employed for reduction of nitro group in the previous work concerning the α-amidosulphones. The use of Zn and hydrochloric acid at room temperature was effective affording the primary amine derivative in moderate yield, demonstrating once more the potential of this strategy as facile access to reductive product of nitro group[75].

[75] L.Serusi, L. Palombi, G. Pierri, A. Di Mola, and A. Massa, *J. Org. Chem.*, **2022**, 87, 13, 8420–8428



Scheme 3.5.3

Then, we focused our attention on the DMM analogue, to achieve acetic ester derivatives in three easy reaction steps, using the strategy suited to for synthesis of novel methylated analogues of PD172938 and Pazinaclone[76].



Scheme 3.5.4

For instance, we scaled up the reaction (1 mmol) to achieve the target molecule bearing DMM in the side chain, affording comparable yield of reaction as 0.15 mmol scale.

After, we performed a saponification of the DMM analogue to reach out the free diacid. The crude mixture was then refluxed in acetonitrile overnight affording the monoacid derivative. The esterification with CH_3I allowed to obtain the monoester analogue in moderate yield.

This proved the versatility of this target molecules suitable for further manipulation and thus showing the utility of the new 1 substituted 3-isoquinolones as important building block for total synthesis of other important biologically active derivatives.

3.5.3 Conclusions

In this paragraph the new cascade methodology for the synthesis of isoquinolin-3-ones have been described. In particular, Mannich initiated cascade reaction of imines derived from 2-formylphenyl acetate in the presence of nitromethane and dimethylmalonate led to novel 1-substituted-isoquinolin-3-ones from good to high yield under catalyst- and solvent-free conditions. Second reactivity of this new class of compounds was

[76] A. Di Mola, G. Nicastro, L. Serusi, R. Filosa, M. Waser and A. Massa , *Molecules*, **2022**, 27, 5647

also investigated with good results which showed the versatility of new isoquinolin-3-ones for further manipulations suitable in synthesis of derivatives meaningful in medicinal chemistry and related fields.

2-Formylphenyl acetate synthesis was also optimized, introducing more environmentally friendly oxidation reactions than the reported Cr(VI)-based reagent, as with the use of NMO or modified Kornblum oxidation.

4 Conclusions

This doctoral PhD thesis had the aim to investigate new cascade reactions for synthesis of new heterocyclic compounds, focusing on new starting materials enabling to promote cascade processes with different nucleophiles. The work carried out in these three years allowed to achieve very important advances in this direction.

The first enantioselective synthesis of 3-substituted isoindolinones with sulfur group was achieved in good yield and good selectivity, thanks to design of new tosylbenzylidenimine. DKR promoted by catalyst was found as important motif of the high selectivity, then new chiral center was found meaningful for leading stereoselective sulfoxidation.

The first cascade reaction with α-amidosulfone and nitromethane allowed to reach out 3-substituted isoindolinones with nitromethyl side chain, overcoming the several limits of previous strategies. The study of second reactivity of this new class of compounds demonstrated the strength of this new synthetic route, manipulating the side chain without any loss in the enantiopurity of the product.

The use of 2-formylbenzonitrile in reaction with DMM has been found a very powerful tool for synthetic pathways to access new methylated analogues of (S)-PD172938 and Panzinaclone. The high selectivity of the tandem process investigated with new synthetic PTC allowed to develop an asymmetric version of this pathway for synthesis and study of new biologically active derivatives.

The use of o-cyanobenzaldehyde in synthesis of phthalidic derivatives was extended to another class of new hybrids with isoxazolidin-5-ones, employing organocatalytic conditions, a very stereoselective process has been achieved. Furthermore, the easy opening isoxazolidin-5-one ring is suitable strategy to access $\beta^{2,2}$-amino acid homologues.

The study of new friendly Mannich initiated cascade reaction with imines derived from 2-formyl phenylacetate led to new class of 1-substituted 3-isoquinolinones. This reaction has the advantage that can be carried out under catalyst free and solvent free conditions with very satisfying results in terms of yield, giving new insights for synthetic routes to reach out this interesting class of compounds. The further manipulation of side chain demonstrated the versatility of this class of molecules to access biologically active derivatives very important in pharmaceutical chemistry and related fields.

In the end it should be underlined once more, the design of new starting materials, and the use of tandem processes and cascade reactions under organocatalytic conditions, are very interesting and useful tools to carry out the aim of this PhD project.

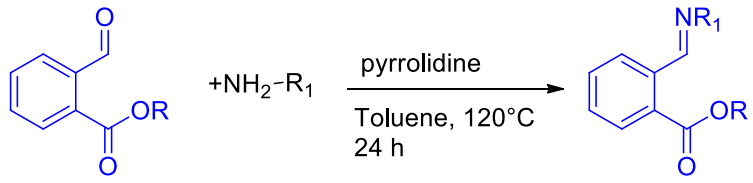
5 Experimental part

5.1 General Information

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, Darmstadt, Germany). The NMR spectra were recorded on Bruker DRX , 600, 400, and 300 MHz spectrometers, Bruker Avance DRX 500 MHz spectrometer, and on a Bruker Avance III 700 MHz. Spectra are reported only for unknown compounds. The following abbreviations are used to indicate the multiplicity in NMR spectra: s-singlet, d-doublet, t-triplet, q-quartet, dd-doublet of doublets, m-multiplet, brs-broad signal. Coupling constants (J) are quoted in Hertz. 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 7T refrigerated actively-shielded superconducting magnet. For ionization of the samples electrospray ionization (ESI) or MALDI was applied.

5.2 2-Carbobenzyloxy N-tosylbenzylidenimine: general procedures and spectroscopic data

General procedure for synthesis of imine 1c-1f.

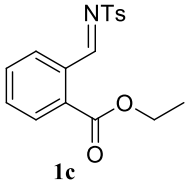


1 **1c-f**

R= Ethyl, $_i$Pr, Benzyl,

R_1= Ts, NPs

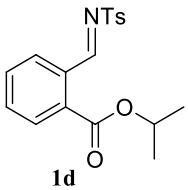
In a ACE tube containing the aldehyde **1** (1.1 mmol), was placed, under nitrogen atmosphere, toluene (3 mL), pyrrolidine (0.11 mmol), molecular sieves (1g/mmol), followed by sulfonyl amine (1.1 mmol). The resulting mixture was stirred for 24 h in a oil bath at 120°C. Then the solvent was removed under reduced pressure. The crude product was purified through crystallization in a solution of Hexane: Ethyl acetate (2:1) affording the corresponding imine **1c-f**.



1c

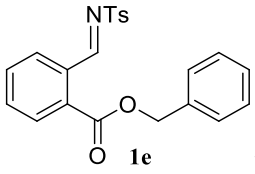
Ethyl-2-((tosylimino)methyl)benzoate (1c). The reaction was performed on 1 g of aldehyde (5.6 mmol) for 24 h. Compound 1c: isolated yield after crystallization 48%, 892 mg, white solid, mp = 129−131 °C; ^{1}H NMR (400 MHz, chloroform-d, 298 K, ppm) δ 9.82 (s, 1H), 8.13−8.10 (m, 1H), 8.03−8.01

(m,1H), 7.91 (d, J = 8.4 Hz, 2H), 7.63−7.59 (m, 2H), 4.42(q, J = 7.2 Hz, 2H), 2.43 (s, 3H), 4.43 (t, J = 7.1 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (75 MHz, chloroform-d, 298 K, ppm) δ 170.2, 165.9, 144.7, 134.7, 133.4, 132.9, 132.8, 132.4, 130.8, 129.8, 129.4, 128.2, 62.1, 21.6, 14.2; HRMS (MALDI-FT ICR) m/z $[M + Na]^+$ calcd for $C_{17}H_{17}NNaO_4S$: 354.0776, found 354.0787; HRMS (MALDI-FT ICR) m/z [M + K]+ calcd for $C_{17}H_{17}KNO_4S$: 370.0515, found 370.0502.



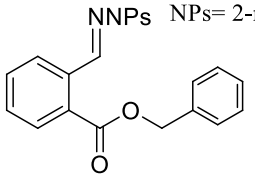
1d

Isopropyl-2-((tosylimino)methyl)benzoate (1d). The reaction was performed with 216 mg of aldehyde (1.12 mmol) for 24 h. Compound 1d: isolated yield after crystallization 65%, 251 mg, white solid, mp = 87−89°C; ^{1}H NMR (400 MHz, chloroform-d, 298 K, ppm) δ 9.83 (s, 1H), 8.11 (d, J = 7.1 Hz, 1H), 8.00 (d, J = 6.5 Hz, 1H), 7.91 (d, J = 7.6 Hz, 2H), 7.61 (t, J = 8.2 Hz, 2H), 7.35 (d, J = 7.05 Hz, 2H), 5.30 (t, J = 6.2 Hz, 1H), 2.43 (s, 3H), 1.41 (d, J = 5.8 Hz, 6H); $^{13}C\{^{1}H\}$ NMR (100 MHz, chloroform-d, 298 K, ppm) δ 192.3, 170.5, 144.8, 135.1, 133.5, 133.1, 132.4, 131.0, 130.0, 129.5, 128.4, 126.6, 70.3, 22.0; HRMS (MALDI-FT ICR) m/z $[M + Na]^+$ calcd for $C_{18}H_{19}NNaO_4S$: 368.0932, found: 368.0939; HRMS (MALDI-FT ICR) m/z [M +K]+ calcd for $C_{18}H_{19}KNO_4S$: 384.0672, found: 384.0673.



1e

Benzyl-2-((tosylimino)methyl)benzoate (1e). The reaction was performed with 271 mg of aldehyde (1.12 mmol) for 24 h. Compound 1e: isolated yield after crystallization 68%, 317 mg. white solid, mp = 126−128 °C; ^{1}H NMR (300 MHz, chloroform-d, 298 K, ppm) δ 9.85 (s, 1H), 8.14−8.11 (m, 1H), 8.06−8.03 (m, 1H), 7.87 (d, J = 8.4 Hz, 2H), 7.62−7.60 (m, 2H), 7.46−7.40 (m, 4H), 7.33 (d, J = 8.4 Hz, 2H), 5.39 (s, 2H), 2.43 (s, 3H); $1^{3}C\{^{1}H\}$ NMR (75 MHz, chloroform-d, 298 K, ppm) δ 170.2, 165.9, 144.8, 135.3, 134.9, 133.5, 132.7, 131.1, 130.0, 129.7, 128.9, 128.8, 128.5, 68.0, 21.8. HRMS (MALDI-FT ICR) m/z $[M + Na]^+$ calcd for $C_{22}H_{19}NNaO_4S$: 416.0932, found: 416.0930; HRMS (MALDI-FT ICR) m/z [M + K]+ calcd for $C_{22}H_{19}KNO_4S$: 432.0672, found: 432.0671.

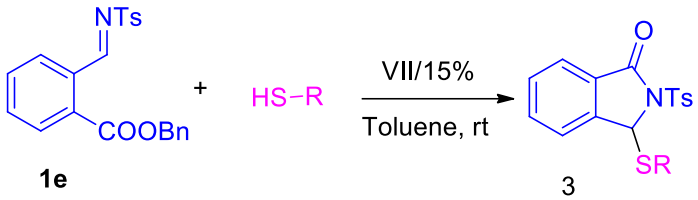


1f

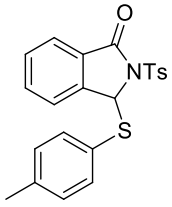
Benzyl 2-(((Naphthalen-2-ylsulfonyl)imino)methyl)benzoate (1f). The reaction was performed with 271 mg of aldehyde (1.12 mmol) for 22 h. Compound 1f: isolated yield after crystallization 20%, 100 mg, pale yellow solid, mp = 126−128 °C; ^{1}H NMR (300 MHz, chloroform-d, 298

K, ppm) δ 9.94 (s, 1H), 8.62 (s, 1H), 8.15−7.90 (m, 6H), 7.67−7.60 (m, 4H), 7.47−7.39 (m, 4H), 5.39 (s, 3H); $^{13}C\{^{1}H\}$ NMR (75 MHz, chloroform-d, 298 K, ppm) δ 170.7, 165.8, 135.4, 135.3, 134.8, 133.6, 133.4, 132.3, 131.1, 130.1, 129.6, 129.4, 129.2, 128.9, 128.8, 128.4, 128.1, 127.7, 123.2, 68.0; HRMS (MALDIFT ICR) m/z [M + Na]+ calcd for $C_{25}H_{19}NNaO_4S$: 452.0932. found: 452.0926; HRMS (MALDI-FT ICR) m/z $[M + K]^+$ calcd for $C_{25}H_{19}KNO_4S$: 468.0672, found: 468.0680.

Typical Procedure for the Reaction of Thiols 2 with the Imine 1e under Organocatalytic Conditions.

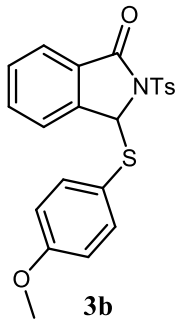


In an ACE tube, imine 1e (19 mg, 0.05 mmol), thiol 2 (0.06 mmol), and organocatalyst VII (3 mg, 0.0075 mmol) were stirred at rt in toluene (0.9 mL). The stirring was prolonged until starting material and/or the intermediate disappeared; then the mixture was directly purified by flash chromatography on silica gel using hexane/ethyl ether (3:1) as an eluent. Rf (hexane/ethyl acetate 3:1) ca. 0.4.



3a

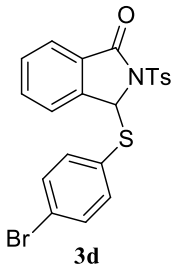
3-(p-Tolylthio)-2-tosylisoindolin-1-one (3a). 83% yield, 17 mg, white solid, mp = 115−118 °C; $[\alpha]^{18}$ = +56.9° (c 0.25, $CHCl_3$); ^1H NMR (300 MHz, chloroform-d, 298 K, ppm) δ 8.24 (d, J = 8.1 Hz, 2H), 7.54 (m, 2H), 7.45−7.38 (m 3H), 7.30−7.29 (m, 1H), 6.65 (d, J= 8.4 Hz, 2H), 6.53−6.48 (m 3H), 2.46 (s, 3H), 2.11 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, chloroform-d, 298 K, ppm) δ 164.5, 146.0, 142.6, 135.9, 134.9, 133.4, 132.0, 130.0, 129.9, 129.2, 128.8, 128.6, 125.2, 124.6, 124.4, 74.5, 21.7, 21.3; HRMS (MALDI-FT ICR) m/z $[M + H]^+$ calcd for $C_{22}H_{20}NO_3S_2$: 410.0879, found: 410.0903. The enantioselectivity was determined by HPLC (Chiralpak IC column, n-hexane/ i-PrOH = 60:40, 1.0 mL/min, t_1 = 12.5 min, t_2 = 18.1 min).



3b

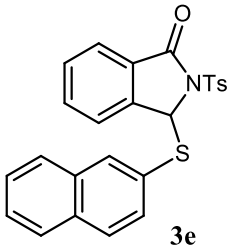
3-((4-Methoxyphenyl)thio)-2-tosylisoindolin-1-one (3b). 80% yield, 17 mg; spectral and analytical data as reported 3-((4-(Methylthio)phenyl)thio)-2-tosylisoindolin-1-one (3c): 50% yield, 11 mg, very dense oil; $[\alpha]^{18}$ = +18.7 (c 0.25, $CHCl_3$); ^1H NMR (400 MHz, chloroform-d, 298 K, ppm) δ 8.23 (d, J = 8.1 Hz, 2H), 7.59−7.53 (m, 2H), 7.46 (d, J = 7.2 Hz, 1H), 7.39 (d, J = 8.1 Hz, 2H), 7.29 (d, J = 7.2 Hz, 1H), 6.71 (d, J = 8.1 Hz, 2H), 6.56−6.53 (m, 2H), 2.46 (s, 3H), 2.31 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, chloroform-d, 298 K, ppm) δ 165.1, 145.5, 142.9, 141.2, 136.3, 136.2, 133.9, 129.7, 129.5, 129.3, 129.2, 125.8, 124.5, 124.2, 123.0, 67.4, 21.9, 15.2; HRMS (MALDI-FT ICR) m/z $[M + H]^+$ calcd for $C_{22}H_{20}NO_3S_3$:

442.0600, found: 442.0616. The enantioselectivity was determined by HPLC (Chiralpak IC column, n-hexane/i-PrOH = 60:40, 1.0 mL/min, t_1 = 17.8 min, t_2 = 27.2 min).



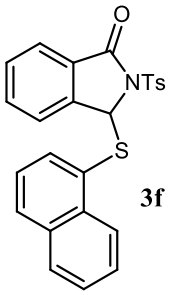
3d

3-((4-Bromophenyl)thio)-2-tosylisoindolin-1-one (3d). 59% yield, 14 mg, white solid, mp = 128−130 °C; $[\alpha]^{18}$ = +58.8° (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, chloroform-d, 298 K, ppm) δ 8.21 (d, J = 8.1 Hz, 2H), 7.59−7.52 (m, 2H), 7.47 (d, J = 7.4 Hz, 1H), 7.38 (d, J = 8.1 Hz, 2H), 7.30 (t, J = 7.4 Hz, 1H), 6.98 (d, J = 8.1 Hz, 2H), 6.54 (s, 1H), 6.47 (d, J = 8.1 Hz, 2H), 2.45 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, chloroform-d, 298 K, ppm) δ 164.7, 145.5, 142.4, 137.1, 135.8, 133.9, 131.6, 129.6, 129.3, 129.2, 128.9, 126.3, 124.4, 124.1, 123.9, 66.8, 21.7; HRMS (MALDI-FT ICR) m/z [M + Na]$^+$ calcd for $C_{21}H_{16}BrNNaO_3S_2$: 497.9627 (100%), found 497.9652 (100%). The enantioselectivity was determined by HPLC (Chiralpak IC column, nhexane/i-PrOH = 60:40, 1.0 mL/min, t_1 = 12.3 min, t_2 = 16.9 min).



3e

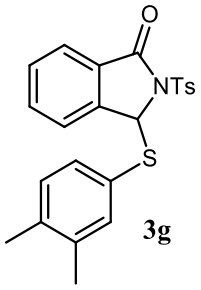
3-(Naphthalen-2-ylthio)-2-tosylisoindolin-1-one (3e). 48% yield, 11 mg, white solid, mp = 69−71 °C; $[\alpha]^{18}$ = +7.5° (c 0.55, $CHCl_3$); ^{1}H NMR (400 MHz, chloroform-d, 298 K, ppm) δ 8.31 (d, J = 7.6 Hz, 2H), 7.60−7.55 (m, 3H), 7.45 (d, J = 7.6, 2H), 7.39−7.29 (m, 5H), 7.21−7.19 (m, 1H), 7.01 (s, 1H), 6.69 (d, J = 9.2 Hz), 6.64 (s, 1H), 2.50 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, chloroform-d, 298 K, ppm) δ 165.0, 145.5,142.9, 136.4, 136.2, 133.9, 133.0, 131.8, 129.8, 129.3, 128.8, 128.4, 128.1, 127.8, 127.5, 127.2, 126.5, 124.8, 124.4, 124.2, 67.3, 21.9; HRMS (ESI-FT ICR) m/z [M + Na]$^+$ calcd for $C_{25}H_{19}NNaO_3S_2$: 468.0699, found: 468.0706. The enantioselectivity was determined by HPLC (Chiralpak IC column, n-hexane/i-PrOH = 60:40, 1.0 mL/min, t_1 = 14.0 min, t_2 = 21.3 min).



3f

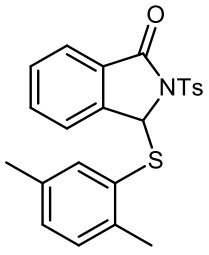
3-(Naphthalen-1-ylthio)-2-tosylisoindolin-1-one (3f). 52% yield, 12 mg, pale yellow solid, mp = 100−102 °C; [α]D 18 = +57.5° (c 0.3, $CHCl_3$); ^{1}H NMR (300 MHz, chloroform-d, 298 K, ppm) δ 8.39

(d, J = 8.8 Hz, 1H), 8.29 (d, J = 8.0 Hz, 2H), 7.65−7.60 (m, 1H), 7.46− 7.32 (m, 5H), 7.16−7.01 (m, 5H), 6.68 (s, 1H), 2.45 (s, 3H); $^{13}C\{^{1}H\}$ NMR (75 MHz, chloroform-d, 298 K, ppm) δ 165.3, 145.5, 142.4, 136.8, 135.3, 135.2, 133.8, 133.2, 130.8, 129.8, 129.2, 129.0, 128.8, 128.3, 126.8, 126.6, 126.4, 126.1, 125.1, 124.1, 124.0, 67.1, 21.9; HRMS (MALDI-FT ICR) m/z $[M + Na]^+$ calcd for $C_{25}H_{19}NNaO_3S_2$: 468.0699, found: 468.0719. The enantioselectivity was determined by HPLC (Chiralpak IC column, n-hexane/i-PrOH = 60:40, 1.0 mL/min, t_1 = 14.5 min, t_2 = 19.8 min).



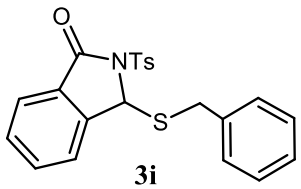
3g

3-((3,4-Dimethylphenyl)thio)-2-tosylisoindolin-1-one (3g). 43% yield, 9 mg, white solid, mp =140−142 °C; $[\alpha]^{18}$ = +50.9° (c 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, chloroform-d, 298 K, ppm) δ 8.29 (d, J= 8.1 Hz, 2H), 7.56 (m, 2H), 7.45−7.40 (m, 3H), 7.29 (m, 1H) 6.58 (d, J = 7.8 Hz, 1H), 6.53 (s, 1H), 6.33(d, J = 7.8 Hz, 1H), 6.18 (s, 1H), 2.47 (s, 3H), 2.00 (s, 3H), 1.81 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, chloroform-d, 298 K, ppm) δ 165.1, 145.4, 143.2, 138.2, 137.0, 136.9, 136.4, 133.7, 133.5, 129.9, 129.8, 129.7, 129.5, 129.2, 129.1, 124.3, 123.8, 67.3, 21.9, 19.5, 19.2; HRMS (ESI-FT ICR) m/z $[M + Na]^+$ calcd for $C_{23}H_{21}NNaO_3S_2$: 446.0855, found: 446.0902. The enantioselectivity was determined by HPLC (Chiralpak IC column, n-hexane/i-PrOH = 60:40, 1.0 mL/min, t_1 = 14.2 min, t_2 = 20.7 min).



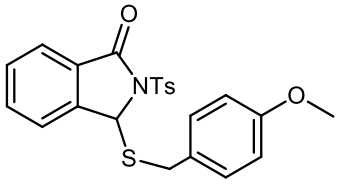
3h

3-((2,5-Dimethylphenyl)thio)-2-tosylisoindolin-1-one (3h). 70% yield, 15 mg, white solid, mp = 140−142 °C; $[\alpha]^{18}$ = −19.1° (sample from the reaction with ent-VII as a catalyst, c = 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, chloroform-d, 298 K, ppm) δ 8.27 (d, J = 8.1 Hz, 2H), 7.50−7.44 (m, 2H), 7.38−7.35 (m, 3H), 7.24−7.21 (m, 1H), 6.76−6.74 (m, 2H), 6.56 (s, 1H), 6.24 (s, 1H), 2.41 (s, 3H), 2.18 (s, 3H), 1.86 (s, 3H); $^{13}C\{^{1}H\}$ NMR (75 MHz, chloroform-d, 298 K, ppm) δ 165.3, 145.4, 143.0, 138.7, 136.0, 135.7, 133.6, 130.2, 129.9, 129.7, 129.5, 127.9, 124.2, 123.7, 67.1, 21.8, 20.7, 20.5; HRMS (MALDI-FT ICR) m/z $[M + H]^+$ calcd for $C_{23}H_{22}NO_3S_2$: 424.1036, found: 424.1033. The enantioselectivity was determined by HPLC (Chiralpak IC column, n-hexane/i-PrOH = 60:40, 1.0 mL/min, t_1 = 11.8 min, t_2 = 19.6 min).



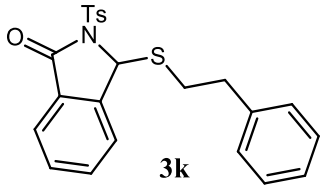
3i

3-(Benzylthio)-2-tosylisoindolin-1-one (3i). 84% yield, 17 mg, white solid, mp = 117−119 °C; $[\alpha]^{18}$ = +30.2° (c 0.15, $CHCl_3$); ^{1}H NMR (400 MHz, chloroform-d, 298 K, ppm) δ 8.21 (d, J = 8.6 Hz, 2H), 7.76 (d, J = 7.3 Hz, 1H), 7.60 (t, J = 7.3 Hz, 1H), 7.47−7.40 (m, 2H), 7.36 (d, J = 8.6 Hz, 2H), 7.18−7.16 (m, 3H), 6.93−6.91 (m, 2H), 6.32 (s, 1H), 3.32 (d, J = 13 Hz, 1H), 3.12 (d, J = 13 Hz, 1H), 2.46 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, chloroform-d, 298 K, ppm) δ 165.1, 145.1, 143.4, 136.1, 134.4, 129.5, 129.2, 128.9, 128.6, 128.4, 127.3, 124.5, 124.1, 65.8, 33.3, 21.7; HRMS (MALDI-FT ICR) m/z [M +K]$^+$ calcd for $C_{22}H_{19}KNO_3S_2$: 448.0438, found: 448.0406. The enantioselectivity was determined by HPLC (Chiralpak IC column, n-hexane/i-PrOH = 60:40, 1.0 mL/min, t_1 = 21.7 min, t_2 = 26.8 min)



3j

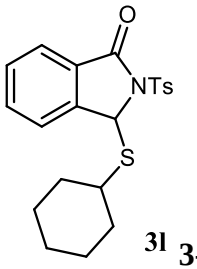
3-((4-Methoxybenzyl)thio)-2-tosylisoindolin-1-one (3j). 91% yield, 20 mg, white solid, mp = 130−132 °C; $[\alpha]^{18}$ = −41.0° (sample from the reaction with ent-VII as a catalyst, c = 0.15, $CHCl_3$); ^{1}H NMR (300 MHz, chloroform-d, 298 K, ppm) δ 8.21 (d, J= 7.5 Hz, 2H), 7.6 (d, J = 7.5 Hz, 1H), 7.62 (t, J = 7.5 Hz, 1H), 7.64−7.59 (m, 2H), 7.36 (d, J = 8.1 Hz, 2H), 6.86 (d, J = 7.5 Hz, 2H), 6.70 (d, J = 7.5 Hz, 2H), 6.30 (s, 1H), 3.75 (s, 3H), 3.30 (d, J = 12.6 Hz, 1H), 3.00 (d, J = 12.6 Hz, 1H), 2.46 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, chloroform-d, 298 K, ppm) δ 165.1, 145.1, 143.4, 136.1, 134.4, 129.5, 129.2, 128.9, 128.6, 128.4, 127.3, 124.5, 124.1, 65.0, 33.3, 21.7; HRMS (MALDI-FT ICR) m/z [M + Na]$^+$ calcd for $C_{23}H_{21}NNaO_4S_2$: 462.0804, found: 462.0826. The enantioselectivity was determined by HPLC (Chiralpak IC column, n-hexane/i-PrOH = 60:40, 1.0 mL/min, t_1 = 20.6 min, t_2 = 23.7 min).



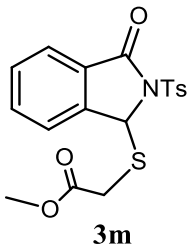
3k

3-(Phenethylthio)-2-tosylisoindolin-1-one (3k). 55% yield, 12 mg, white oil; $[\alpha]^{18}$ = −16.0° (sample from the reaction with ent-VII as a catalyst, c = 0.55, $CHCl_3$); ^{1}H NMR (300 MHz, chloroform-d, 298 K, ppm) δ 8.19 (d, J = 7.8 Hz, 2H), 7.79 (d, J = 7.1 Hz, 1H), 7.70−7.65 (m, 1H), 7.56 (d, J = 7.8 Hz, 1H), 7.51−7.46 (m, 1H), 7.34 (d, J = 7.8 Hz, 2H), 7.19−7.16 (m, 2H), 6.81−6.78 (m, 2H), 6.37 (s, 1H), 2.43−2.35 (m, 5H), 2.00−1.97 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, chloroform-d, 298 K, ppm) δ 165.2, 145.3, 143.5, 139.6, 136.3, 134.6, 129.7, 129.6, 129.6, 128.7, 128.5, 128.3, 126.6, 124.7, 124.1, 65.2, 34.9, 29.1, 21.8; HRMS (MALDI-FT ICR) m/z [M + Na]$^+$ calcd for $C_{23}H_{21}NNaO_3S_2$: 446.0855, found:

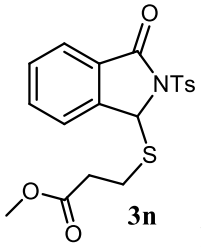
446.0872. The enantioselectivity was determined by HPLC (Chiralpak IC column, n-hexane/i-PrOH = 60:40, 1.0 mL/min, t_1 = 19.6 min, t_2 = 24.6 min).



3l **3-(Cyclohexylthio)-2-tosylisoindolin-1-one (3l).** 61% yield, 12 mg, white solid, mp = 152−154 °C; $[\alpha]^{18}$ = −63.3° (sample from the reaction with ent-VII as a catalyst, c = 0.15, $CHCl_3$); ^{1}H NMR (300 MHz, chloroform-d, 298 K,ppm) δ 8.16 (d, J = 8.6 Hz, 2H), 7.78 (d, J= 8.0 Hz, 1H), 7.67 (t, J = 7.5 Hz, 1H), 7.59 (d, J = 7.5 Hz, 1H), 7.47 (t, J = 7.5 Hz, 1H), 7.34 (d, J = 8.0 Hz, 2H), 6.39 (s, 1H), 2.52−2.43 (m, 4H), 1.60−1.44 (m, 6H), 1.10−1.08 (m, 5H); ^{13}C{^{1}H} NMR (75 MHz, chloroform-d, 298 K, ppm) δ 165.5, 145.2, 144.5, 136.5, 134.4, 129.5, 129.3, 128.8, 124.7, 124.5, 65.4, 43.2, 34.9, 33.5, 26.0, 25.8, 25.6, 21.8; HRMS (MALDI-FT ICR) m/z [M + H]$^+$ calcd for $C_{21}H_{24}NO_3S_2$: 402.1192, found: 402.1206. The enantioselectivity was determined by HPLC (Chiralpak IC column, n-hexane/i-PrOH = 60:40, 1.0 mL/min, t_1 = 15.5 min, t_2 = 26.9 min).

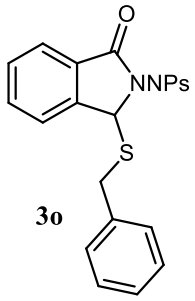


3m **Methyl 2-((3-Oxo-2-tosylisoindolin-1-yl)thio)acetate (3m).** 83% yield, 18 mg, very dense oil; $[\alpha]^{18}$ = +26.9 (c 0.6, $CHCl_3$); ^{1}H NMR (300 MHz, chloroform-d, 298 K, ppm) δ 8.15 (d, J = 8.5 Hz, 2H), 7.78 (d, J = 7.5 Hz, 1H), 7.68 (m, 2H), 7.52−7.50 (m, 1H), 7.35 (d, J= 8.5 Hz, 2H), 6.51 (s, 1H), 3.47 (s, 3H), 3.20 (d, J = 15 Hz, 1H), 2.84 (d, J = 15 Hz, 1H), 2.43 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, chloroform-d, 298 K, ppm) δ 169.8, 165.0, 145.3, 142.6, 135.6, 134.4, 129.8, 129.5, 128.6, 124.6, 124.5, 65.2, 52.5, 31.3, 21.7; HRMS (MALDI-FT ICR) m/z [M + Na]$^+$ calcd for $C_{18}H_{17}NNaO_5S_2$: 414.0440, found: 414.0466. The enantioselectivity was determined by HPLC (Chiralpak IC column, n-hexane/i-PrOH = 50:50, 1.0 mL/ min, t_1 = 21.5 min, t_2 = 28.1 min).



3n **Methyl 3-((3-Oxo-2-tosylisoindolin-1-yl)thio)propanoate (3n).** 90% yield, 18 mg, very dense oil; $[\alpha]^{18}$ = +27.8 (c 0.75, $CHCl_3$); ^{1}H NMR (300 MHz, chloroform-d, 298 K, ppm) δ 8.16 (d, J = 8.7

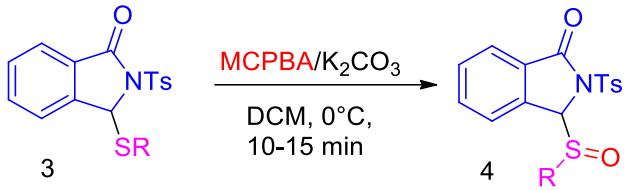
Hz, 2H), 7.82−7.77 (m, 1H), 7.73−7.68 (m, 1H), 7.62−7.60 (m, 1H), 7.53−7.48 (m, 1H), 7.35 (d, J = 8.1 Hz, 2H), 6.38 (s, 1H), 3.60 (s, 3H), 2.43 (s, 3H), 2.14−2.12 (m, 4H); $^{13}C\{^{1}H\}$ NMR (75 MHz, chloroform-d, 298 K, ppm) δ 171.5, 165.0, 145.2, 143.2, 135.9, 134.5, 129.7, 129.5, 128.5, 126.4, 124.7, 124.1, 65.2, 51.8, 33.5, 23.2,21.6; HRMS (MALDI-FT ICR) m/z $[M + Na]^+$ calcd for $C_{19}H_{19}NNaO_5S_2$: 428.0597, found 428.06095. The enantioselectivity was determined by HPLC (Chiralpak IC column, n-hexane/i-PrOH = 60:40, 1.0 mL/min, t_1 = 23.7 min, t_2 = 30.5 min).



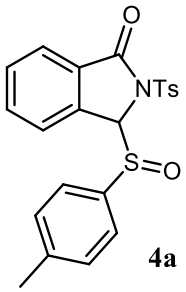
3o

3-(Benzylthio)-2-(naphthalen-2-ylsulfonyl)isoindolin-1-one (3o). 86% yield, 19 mg, white solid, mp = 151−153 °C; $[\alpha]^{18}$ = +32.1° (c 0.75, $CHCl_3$); ^{1}H NMR (400 MHz, chloroform-d, 298 K, ppm) δ 8.89 (s,1H), 8.36−8.34 (m, 1H), 8.05−8.00 (m, 2H), 7.95 (d, J = 7.7 Hz, 1H), 7.79 (d, J = 7.7 Hz, 1H), 7.72−7.68 (m, 1H), 7.66−7.61 (m, 2H), 7.49−7.46 (m, 2H), 7.09−7.06 (m, 1H), 7.00 (t, J = 7.7 Hz, 2H), 6.69 (d, J = 7.7 Hz, 2H), 6.41 (s, 1H), 3.14 (d, J = 12.2 Hz, 1H), 3.04 (d, J = 12.2 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (75 MHz, chloroform-d, 298 K, ppm) δ 165.3, 143.5, 136.1, 135.9, 135.7, 134.7, 132.1, 130.8, 130.0, 129.7, 129.6, 129.3, 129.0, 128.5, 128.1, 127.7, 127.3, 124.8, 124.2, 123.2, 65.4, 33.3; HRMS (MALDI-FT ICR) m/z $[M + Na]^+$ calcd for $C_{25}H_{19}NNaO_3S_2$: 468.0699, found: 468.0732. The enantioselectivity was determined by HPLC (Chiralpak IC column, n-hexane/i-PrOH = 60:40, 1.0 mL/min, t_1 = 15.3 min, t_2 = 18.9 min).

Typical Procedure for the Synthesis of 3-Sulphinyl Isoindolinones 4.

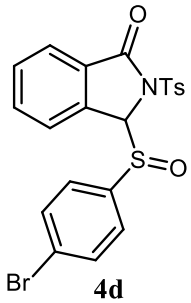


In a round-bottom flask, MCPBA (0.12 equiv), K2CO3 (14 mg, 0.12 equiv), and starting isoindoninone N,S-acetal 3 (0.1 mmol) were stirred at 0 °C in CH2Cl2 (16 mL). The reaction was monitored by TLC and prolonged until starting material 3 disappeared (10−15 min). The mixture was then evaporated, and the crude material was purified by flash chromatography on silica gel with hexane/ethyl acetate 3:1. Rf ca. 0.2 (hexane/ethyl acetate 3:1).



4a

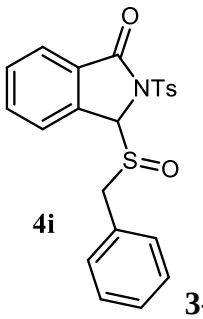
3-(p-Tolylsulfinyl)-2-tosylisoindolin-1-one (4a). The reaction, performed on 40 mg of 3a, yielded the product in an 86% yield: 36 mg, white solid, mp = 66−68 °C; $[\alpha]^{18}$ = +181.9 (c 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, chloroform-d, 298 K, ppm) δ 8.09 (d, J = 8.5 Hz, 2H), 7.87 (d, J = 7.5 Hz, 1H), 7.63−7.59 (m, 1H), 7.42−7.32 (m, 4H), 6.85 (d, J = 8.5 Hz, 2H), 6.71 (d, J = 8.5 Hz, 2H), 6.21 (s, 1H), 2.44 (s, 3H), 2.20 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, chloroform-d, 298 K, ppm) δ 164.5, 146.0, 142.6, 135.9, 135.0, 133.4, 132.0, 129.9, 128.8, 128.6, 125.2, 124.6, 124.4, 74.6, 21.7, 21.3; FTIR-ATR: 1735, 1168, 1053, 659 (cm−1, film); HRMS (MALDI-FT ICR) m/z $[M + Na]^+$ calcd for $C_{22}H_{19}NNaO_4S_2$: 434.0491, found: 434.0504. The enantioselectivity was determined by HPLC (Chiralpak AD column, n-hexane/i-PrOH = 70:30, 0.8 mL/min, t_1 = 15.3 min, t_2 = 20.0 min)



4d

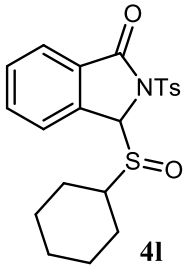
3-((4-Bromophenyl)sulfinyl)-2-tosylisoindolin-1-one (4d, CCDC 2073548). The reaction, performed on 47 mg of 3d, yielded the product in a 77% yield: 37 mg, pale pink solid, mp =48−50 °C; $[\alpha]^{18}$ = +97.4° (c 0.15, $CHCl_3$); ^{1}H NMR (300 MHz, chloroform-d, 298 K, ppm) δ 8.08 (d, J = 8.1 Hz, 2H), 7.85 (d, J = 8.1 Hz, 1H), 7.65−7.62 (m, 1H), 7.40 (s, 3H), 7.20 (d, J = 8.7 Hz, 2H), 6.76 (d, J = 8.7 Hz, 2H), 6.21

(s, 1H), 2.45 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, chloroform-d, 298 K, ppm) δ 164.5, 146.4, 135.8, 135.0, 134.9, 133.8, 131.6, 130.5, 130.2, 129.8, 128.9, 127.0, 126.8, 124.9, 124.7, 74.7, 21.9. FTIR-ATR: 1742, 1170, 1056, 661 (cm−1, film); HRMS (MALDI-FT ICR) m/z $[M + H]^+$ calcd for $C_{21}H_{17}BrNO_4S_2$: 489.9704, found: 489.1906. The enantioselectivity was determined by HPLC (Chiralpak AD column, n-hexane/i-PrOH = 70:30, 0.8 mL/min, t_1 = 15.1 min, t_2 = 20.2 min).



4i

3-(Benzylsulfinyl)-2-tosylisoindolin-1-one (4i). The reaction, performed on 40 mg of 3i, yielded the product in an 86% yield: 36 mg, white solid, mp = 139−141 °C; $[\alpha]^{18}$ = +83.9° (c 0.6, $CHCl_3$); ^{1}H NMR (300 MHz, chloroform-d, 298 K, ppm) δ 8.09 (d, J = 6.9 Hz, 2H), 7.93 (d, J = 7.7 Hz, 2H), 7.80−7.76 (m, 2H), 7.66 (t, J = 7.7 Hz, 2H), 7.47 (s, 1H), 7.39 (d, J = 7.7 Hz, 2H), 6.86 (d, J = 6.9 Hz, 2H), 6.26 (s, 1H), 3.06 (d, J = 12.5 Hz, 1H), 2.67 (d, J12.5 Hz, 1H), 2.48 (s, 3H); $^{13}C\{^{1}H\}$ NMR (75 MHz, chloroform-d, 298 K, ppm) δ 165.0, 146.0, 137.1, 135.1, 134.6, 130.7, 130.0, 129.6, 129.0, 128.8, 128.6, 128.4, 125.4, 124.9, 72.7, 52.0, 21.7; HRMS (MALDI-FT ICR) m/z $[M + Na]^+$ calcd for $C_{22}H_{19}NNaO_4S_2$; 448.0648, found: 448.0666. The enantioselectivity was determined by HPLC (Chiralpak AD column, n-hexane/i-PrOH = 70:30, 0.8 mL/min, t_1 = 24.4 min, t_2 = 28.6 min).



4l

3-(Cyclohexylsulfinyl)-2-tosylisoindolin-1-one (4l). The reaction, performed with 40 mg of 3i, yielded the product in an 88% yield: 37 mg, white solid, mp = 113−115 °C; $[\alpha]^{18}$ = −122.9° (sample obtained from starting 3 as obtained using ent-VII as a catalyst, c = 0.35, $CHCl_3$); ^{1}H NMR (300 MHz, chloroform-d, 298 K, ppm) δ 8.05 (d, J = 7.7 Hz, 2H), 7.87 (d, J = 7.7 Hz, 2H), 7.69 (t, J = 7.7 Hz, 1H), 7.60 (t, J = 7.7 Hz, 1H), 7.35 (d, J = 7.7 Hz, 2H), 6.15 (s, 1H), 2.42 (s, 3H), 2.02−1.92 (m, 1H), 1.65−1.59 (m, 2H), 1.48−1.43 (m, 2H), 1.25−1.21 (m, 6H); $^{13}C\{^{1}H\}$ NMR (75 MHz, chloroform-d, 298 K, ppm) δ 165.5, 146.0, 138.3, 135.2, 134.5, 130.7, 129.9, 129.6, 128.8, 125.4, 125.0, 73.0, 54.5, 27.6, 25.4, 25.3, 25.2, 25.0, 21.8; HRMS (MALDI-FT ICR) m/z $[M +K]^+$ calcd for $C_{21}H_{23}KNO_4S_2$: 456.0700, found: 456.0928. The enantioselectivity was determined by HPLC (Chiralpak AD column, n-hexane/i-PrOH = 70:30, 0.8 mL/min, t_1 = 15.9 min, t_2 = 17.2 min).

Single crystal X-ray diffraction

Single crystals suitable for X-ray diffraction analysis of compound **4d** were obtained by crystallization from dichloromethane/hexane solution. The X-ray molecular structure is shown in Figure 2 of the main article and herein (Figure S2).

A suitable crystal (0.48 x 0.37 x 0.32 mm) was glued on a fiber glass and measured at 296 K with a Bruker D8 QUEST diffractometer equipped with a PHOTON100 detector using Cu$K\alpha$ radiation (λ = 1.54178 Å). Indexing was performed using APEX3. Data integration and reduction were performed using SAINT. Absorption correction was performed by multi-scan method in SADABS.

The structure was solved by Direct Methods using SHELXT2014 and refined by means of full matrix least-squares based on F^2 using the program SHELXL.

Non-hydrogen atoms were refined anisotropically, hydrogen atoms were positioned geometrically and included in structure factors calculations, but not refined. Crystal structures were drawn using OLEX2. Crystal data and refinement details are reported in Table S4.

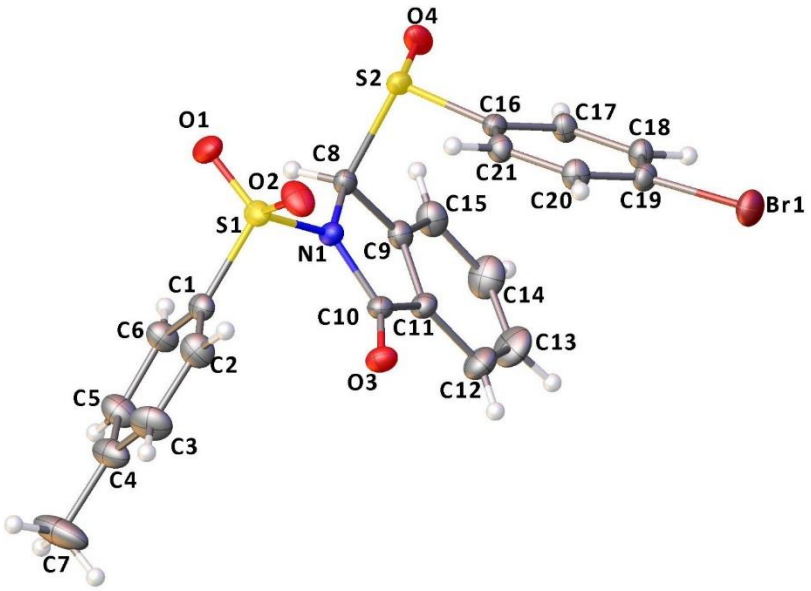


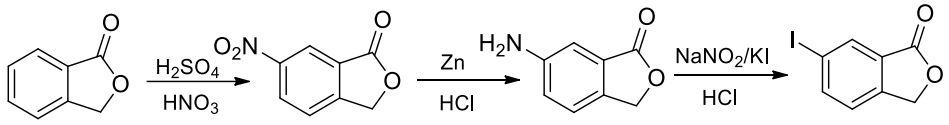
Figure S2. X-ray molecular structure (ORTEP) of compound **4d** (observed configuration: C_S,S_R). Ellipsoids drawn at 20% probability. Also reported in Figure 2 of the main article.

Table S4. Crystal data and refinement details for compound **4d**.

Formula	$C_{21}H_{16}BrNO_4S_2$
FW	490.38
system	orthorhombic
space group	$P2_12_12_1$
a (Å) b (Å) c (Å)	9.2101(14) 9.9662(16) 23.163(6)
V (Å^3)	2126.1(7)
Z	4
D_x (g cm^{-3})	1.532
μ (mm^{-1})	4.709
F_{000}	992
$R1$ (3880 $I > 2\sigma_I$)	0.0347
${}_wR2$ (all data)	0.0947
N. of reflections	3961
N. of parameters	263
GooF	1.072
Flack parameter	0.047(8)
ρ_{min}, ρ_{max} (eÅ^{-3})	-0.537, 0.552

5.3 α-Amidosulfones: general procedures and spectroscopic data

Procedures for the synthesis of 6-iodophthalide



Synthesis of 6-nitrophthalide: Phthalide (2.0 g, 1.0 eq., 15.0 mmol) was dissolved in fuming nitric acid (2.0 mL) and concentrated sulfuric acid (2.3 mL) at 0 °C. The ice bath was then removed and the reaction stirred for 12 h. The reaction was then poured into an ice-H2O bath and collected via filtration to give the crude product as a white solid. Recrystallisation from Hexane/CHCl3 gave the title compound as white crystals (Yield= 1.630 mg, 61%). ^{1}H NMR (400 MHz, CDCl3): δ 8.77 (d, J= 1.8 Hz, 1H), 8.59 (d, J= 8.3 Hz, 1H), 7.72 (d, J= 8.4 Hz, 1H), 5.46 (s, 2H). Mp and the obtained spectroscopic data were found in agreement with literature[77]

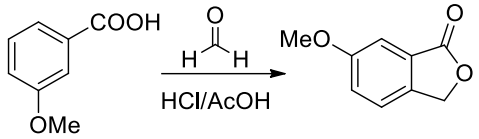
Synthesis of 6-aminophthalide: To a solution of 6-nitrophthalide (1.0 g, 1 eq., 5.58 mmol) in methanol (33.0 mL) Zn (1.450 g, 4 eq., 22.3 mmol) and 37% HCl (6.25 mL) were added dropwise at 0° (ice bath) and the mixture stirred for 2 h. The mixture was then basified with sodium hydroxide and filtered. The aqueous layer was extracted with Ethyl acetate two times, dried in vacuo to yield the corresponding 6-aminophthalide as yellow solid. (Yield= 830 mg, 99%). ^{1}H NMR (600 MHz, DMSO-d6): δ 7.24 (d, J= 7.8 Hz, 1H), 6.98 (dd, J_1= 8.4, J_2= 1.2 Hz, 1H), 6.92 (s, 1H), 5.46 (s, 2H), 5.18 (s, 2H). Mp and the obtained spectroscopic data were found in agreement with literature[78].

Synthesis of 6-iodophthalide: In an ice bath a solution of NaNO2 (610 mg, 1.2 eq., 6.5 mmol) in H2O (1.2 mL) was added dropwise to a suspension of 6-aminophthalide (800 mg, 1.0 eq., 5.4 mmol) in 37% HCl (3.5 mL) and the resulting mixture was stirred for 25 min at 0°C. Then, a solution of KI (4.5 g, 5.0 eq., 27.0 mmol) in H2O (4.6 mL) was added dropwise. The mixture was stirred at room temperature for 18 h. Then, the aqueous suspension was extracted with Ethyl acetate and the combined organic layers were washed with saturated aq. Na2S2O3 and brine (14.0 mL), dried over Na2SO4 and concentrated in vacuo. The residue was purified by silica gel column chromatography eluting with CHCl3 to obtain the product as white solid. (Yield= 900 mg, 65%). ^{1}H NMR (300 MHz, CDCl3) δ 8.26 (d, J= 1.5 Hz, 1H), 7.99 (dd, J_1= 8.0 Hz, J_2= 1.5

[77] Santoso, K. T.; Cheung, C. Y.; Hards, K.; Cook, G. M.; Stocker, B. L.; Timmer. M. S. M., *Chem Asian J.*, **2019**, 14, 1278-1285
[78] Du, J.; Chen, J.; Xia, H; Zhao, Y.; Wang, F.; Liu, H.; Zhou, W.; Wang, B., *Chem. Cat. Chem*., **2020**, 12, 2426-2430

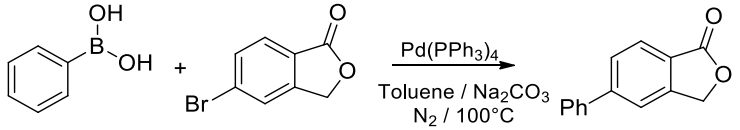
Hz, 1H), 7.30 (d, J= 8.0 Hz, 1 H), 5.29 (s, 2 H). Mp and the obtained spectroscopic data were found in agreement with literature[79].

Procedure for the synthesis of 6-methoxyphthalide



To a solution of 3-methoxybenzoic acid (1.520 g, 1.0 eq., 10.0 mmol) in glacial acetic acid (5 mL), 37% HCl (7.5 mL) and 30% formaldehyde (3 mL, 4.0 eq., 40.0 mmol) were added, and the reaction mixture was stirredat 100°C for 1 h in an oil bath. After cooling, a saturated solution of $NaHCO_3$ was added until pH=7. The resulting mixture was extracted with CH_2Cl_2 twice, the combined organic layers were dried over Na_2SO_4 andconcentrated under reduced pressure. The residue was purified by column chromatography on silica gel (Hexane/Ethyl acetate, 7:1) to afford 6-methoxyphthalide as a gum. (Yield= 700 mg, 43%). ^{1}H NMR (400 MHz,$CDCl_3$) δ 7.36 (d, *J*= 8.4 Hz, 1H), 7.28 (d, *J*= 2.2 Hz, 1H), 7.23 (dd, J_1= 8.4, J_2= 2.2 Hz, 1H), 5.24 (s, 2H), 3.84 (s, 3H). The obtained spectroscopic data were found in agreement with literature[80].

Procedure for the synthesis of 5-phenylphthalide



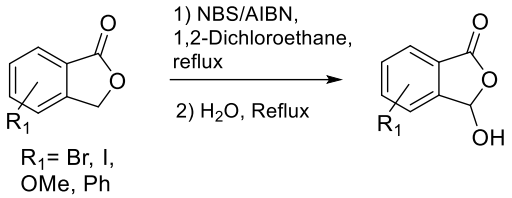
Phenylboronic acid (340 mg, 1.0 eq., 2.8 mmol), 5-bromophthalide (600 mg, 1.0 eq., 2.88 mmol) and tetrakis (triphenylphosphine)palladium 1(0) ($Pd(PPh_3)_4$) (130 mg, 4.0 mol%) were stirred in toluene (2.8 mL) and 2 MNa_2CO_3 solution (2.24 mL) at 100°C in an oil bath for 3 h under nitrogen atmosphere. Then, the mixture wasextracted with Ethyl acetate three times. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (Petroleum ether/Ethyl acetate, 8:1) affording 5-phenylphthalide as white solid (Yield= 600 mg, 99%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, *J*= 7.8 Hz, 1H), 7.77 (d, *J*= 7.9 Hz, 1H), 7.65 (m, 1H), 7.45 (m, 5H), 5.38 (s, 2H). Mp and the obtained spectroscopic data were found in agreement with literature[81].

[79] Beck, D. E.; Abdelmalak, M.; Wei, L.; P. V. Narasimha Reddy; Tender, G. S.; O'Neill, E.; Agama, K.; Marchand, C.; Pommier, Y.; Cushman, M., *J. Med. Chem.*, **2015**, 58, 3997-4015

[80] Vila, N.; Besada, P.; Viña, D.; Sturlese, M.; Moro, S.; Terán, C., *RSC Adv.*, **2016**, 6, 46170-46185

[81] Wu, S.; Liu, N.; Dong, G.; Ma, L.; Wang, S.; Shi, W.; Fang, K.; Chen, S.; Li, J.; Zhang, W.; Sheng, C.; Wang, W., *Chem. Commun.*, **2016**, 52, 9593-9596.

Typical procedure for the synthesis of 3-Hydroxy Phthalide derivates



A mixture of phthalide (1.0 eq., 2.5 mmol), *N*-bromosuccinimide (NBS, 1.1 eq., 2.75 mmol) and azobisisobutyronitrile (AIBN, 0.04 eq., 0.10 mmol) in 1,2-dichloroethane (15.0 mL) was refluxed for 1-6 h in an oil bath. The reaction mixture was kept in an ice bath for 2 h and then filtered. The solvent was removed under reduced pressure and the crude was suspended in water (7.0 mL) and the resulting mixture was refluxed for 1 h. The reaction mixture was cooled to room temperature and extracted with Ethyl acetate three times. The combined organic phases were dried and concentrated under reduced pressure to give 3-hydroxyphthalide derivatives, which are known compounds[61-63-82].

5-bromo 3-hydroxy phthalide[63]. White solid (470 mg, 82%). **^{1}H NMR** (300 MHz, DMSO-d_6) δ 8.28 (d, *J*= 4.1 Hz,1H), 7.96-8.00 (m, 1H), 7.63 (*d*, *J*= 7.7 Hz, 2H), 6.66 (d, *J*= 4.6 Hz, 1H).

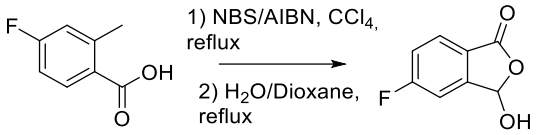
3-hydroxy 6-methoxy phthalide[64]. Reaction carried out on 4 mmol of respective phthalide**.** White solid (597 mg, 83%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.54 (s, 1H), 7.29 (s, 2H), 6.53 (s, 1H), 5.57 (s, 1H), 3.88 (s, 3H)

3-hydroxy 6-iodophthalide[61]. White solid (495 mg, 72%).**^{1}H NMR** (300 MHz, DMSO-d_6) δ 8.26 (d, *J*= 7.0 Hz, 1H), 8.06-8.02 (m, 2H), 7.49 (d, *J*= 7.8 Hz, 1 H), 6.64 (d, *J*= 7.6 Hz, 1 H).

3-hydroxy 5-phenylphthalide[63]. White solid (276 mg, 49%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.98 (d, *J*= 7.6 Hz, 1H), 7.86 (d, *J*= 6.9 Hz, 2H), 7.66 (d, *J*= 7.6 Hz, 3H), 7.53 (t, *J*= 7.0 Hz, 2H), 7.47-7.49 (m, 1H), 6.71 (s, 1H).

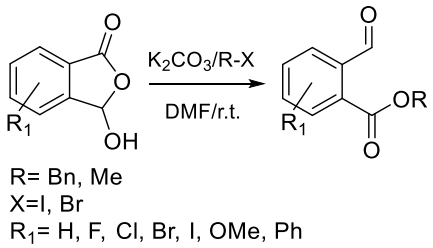
[82] Zhang, Y.; Ao, Y. F.; Huang, Z. T.; Wang, De X.; Wang, M. X.; Zhu, J., *Angew. Chem. Int. Ed*., **2016**, 55, 5282-5285.

Procedure for the synthesis of 5-fluoro-3-hydroxyphthalide.



N-bromosuccinimide (1.440 mg, 2.5 eq., 8.1 mmol) and azobisisobutyronitrile (20 mg, 0.04 eq., 0.12 mmol) were added to a suspension of 4-fluoro-2-methylbenzoic acid (500 mg, 1.0 eq., 3.24 mmol) in CCl_4 (13.0 mL) and refluxed for 4-6 h in an oil bath. Then the mixture was cooled to room temperature. and filtered. The resulting organic solution was evaporated in *vacuo*, the residue dissolved in a mixture of water/dioxane (1:1,7.5 mL/7.5 mL) and refluxed for 8 h. Then dioxane was removed under reduced pressure and the aqueous layer extracted with Ethyl acetate twice to afford the resulting 5-fluoro-3-hydroxyphthalide as white solid. (Yield= 495 mg, >99%). **^{1}HNMR** (400 MHz, DMSO-d_6) δ 8.30 (d, J= 7.3 Hz, 1H), 7.90 (dd, J_1= 8.1, J_2= 4.8 Hz, 1H), 7.54 (dd, J_1= 8.0, J_2= 1.6 Hz, 1H), 7.55-7.44 (m, 1H), 6.65 (d, J= 7.1 Hz, 1H). Mp and the obtained spectroscopic data were found in agreement with literature[64].

Typical procedure for the synthesis of carboalkoxy-benzaldehyde derivattives.



K_2CO_3 (0.6 eq.) and Benzyl Bromide or iodomethane (1.2 eq.) were added to a suspension of 3-hydroxyphthalide (1.0 eq.) in DMF (0.5 M). The resulting mixture was stirred for 16-18 h. Then the mixture was extracted with Ethyl acetate and water and the resulting organic layer washed with brine. The organic

layer was dried over Na_2CO_3 and evaporated under vacuo. The mixture was directly purified by flash chromatography on silica gel (Hexane/Ethyl acetate, 5:1) to give the resulting 2-formylbenzoate esters **a-h.**

Benzyl 2-formylbenzoate. (a)[83]

Following the general procedure using 6.7 mmol of the respective of 3-hydroxyphthalide, the title compoundwas obtained as a colorless oil in 87% yield (1.4 g).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.60 (s, 1H), 7.99-7.96 (m, 1H), 7.93-7.90 (m, 1H), 7.63-7.58 (m, 2H), 7.44-7.34(m, 5H), 5.40 (s, 2H).

Methyl 2-formylbenzoate. (a-1)[65]

Following the general procedure using 5.0 mmol of the respective of 3-hydroxyphthalide, the title compound was obtained as a colorless oil in 95% yield (780 mg).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 10.60 (s, 1H), 7.98-7.90 (m, 2H), 7.66-7.62 (m, 2H), 3.96 (s, 3H)

Benzyl 4-fluoro-2-formylbenzoate. (c)

Following the general procedure using 2.2 mmol of the respective of 3-hydroxyphthalide, the title compound was obtained as a colorless oil in 80% yield (454 mg).

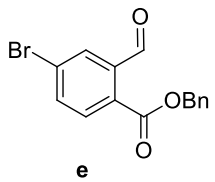
^{1}H NMR: (400 MHz, $CDCl_3$): δ 10.66 (s, 1H), 8.08 (dd, J_1= 5.5 Hz, J_2= 2.9 Hz, 1H), 7.62 (dd, J_1= 5.5 Hz, J_2= 2.9 Hz, 1H), 7.46-7.28 (m, 6H), 5.41 (s, 2H).**^{13}C NMR:** (75 MHz, $CDCl_3$): δ 190.9, 165.2, 140.3, 135.3, 133.7 ($J_{C\text{-}F}$= 8.5 Hz), 128.9, 119.9 ($J_{C\text{-}F}$= 22.2 Hz), 115.4 ($J_{C\text{-}F}$= 22.2 Hz), 67.9.**HRMS (ESI-FT ICR):** *m/z* calcd for $C_{15}H_{11}FO_3$ $[M+Na]^+$= 281.0595, found: 281.0578.

Benzyl 5-chloro-2-formylbenzoate. (d)[65]

Following the general procedure using 3.0 mmol of the respective of 3-hydroxyphthalide, the title compound was obtained as a colorless oil in 94% yield (772 mg).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.56 (s, 1H), 7.93 (d, J = 2.0 Hz, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.56 (dd, J_1= 8.4 Hz, J_2= 2.0 Hz, 1H), 7.44-7.35 (m, 5H), 5.39 (s, 2H).

Benzyl 4-bromo-2-formylbenzoate. (e)



e

Following the general procedure using 2.0 mmol of the respective of 3-hydroxyphthalide, the title compound was obtained as a colorless oil in 87% yield (555 mg).

[83] Sharique, M.; Tamba, U. K. *N*-Heterocyclic carbene based catalytic platform for Hauser–Kraus annulations *Chem.Sci.* **2020**,11, 7239-7243. (b) Longhui, Y.; Jun L.; Hongyu W.; Lijun, X.; Wu, Y.; a Zheng, C.; Gang Z., *Adv. Synth. Catal.* **2022**, 302-306. (c) Mirabdolbaghi, R.; Dudding, T., *Org. Lett.* **2012**, *14*, 3748-3751.

^{1}H NMR: (300 MHz, Chloroform-*d*, 298 K, ppm) δ 10.61 (s, 1H), 8.03 (d, *J*=2.2 Hz, 1H), 7.88 (d, *J*=7.2 Hz, 1H), 7.73 (dd, J_1=7.2 Hz, J_2=2.2 Hz, 1H), 7.44-7.37 (m, 5H), 5.40 (s, 2H). **^{13}C NMR**: (75 MHz, Chloroform-*d*, 298 K, ppm) δ 190.8, 165.4, 138.7, 135.9, 135.2, 131.6, 130.5, 128.9, 128.7, 127.9, 68.0. **HRMS (MALDI-FT ICR):** *m/z* calcd for $C_{15}H_{11}BrO_3$ $[M+Na]^+$= 340.9789, found: 340.9781.

Benzyl 2-formyl-5-methoxybenzoate. (f)[65]

Following the general procedure using 3.0 mmol of the respective of 3-hydroxyphthalide, the title compound was obtained as a colorless oil in 35% yield (283 mg).

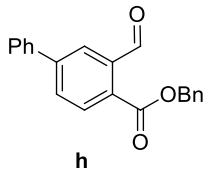
1H NMR ($CDCl_3$, 400 MHz) δ 10.54 (s, 1H), 7.82 (d, *J*= 8.0 Hz, 1H), 7.74 (s, 1H), 7.46-7.31 (m, 6H), 5.37 (s, 2H), 3.88 (s, 3H)

Benzyl 2-formyl-4-iodobenzoate. (g)[65]

Following the general procedure using 1.0 mmol of the respective of 3-hydroxyphthalide, the title compound was obtained as a colorless oil in 85% yield (311 mg).

1H NMR ($CDCl_3$, 400 MHz) δ 10.57 (s, 1H), 8.33 (d, *J*=1.7 Hz, 1H), 8.01 (dd, J_1= 8.2, J_2= 1.5 Hz, 1H), 7.64 (d, *J*=8.2 Hz, 1H), 7.48-7.34 (m, 5H), 5.43 (s, 2H).

Benzyl 3-formyl-[1,1'-biphenyl]-4-carboxylate. (h)

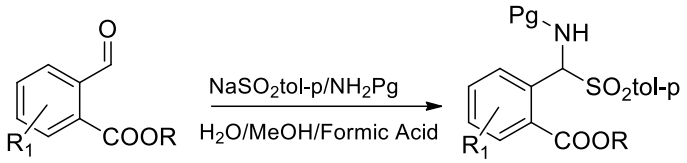


h

Following the general procedure using 1.0 mmol of the respective of 3-hydroxyphthalide, the title compound was obtained as colorless oil in 63% yield (200 mg).
^{1}H NMR: (300 MHz, Chloroform-*d*, 298 K, ppm) δ 10.73 (s, 1H), 8.17 (d, *J*=1.9 Hz, 1H), 8.10 (d, *J*=6.9 Hz, 1H), 7.85(dd, J_1=6.9 Hz, J_2=1.9 Hz, 1H), 7.66-7.63 (m, 2H), 7.49-7.38 (m, 8H), 5.44 (s, 2H).**^{13}C NMR:** (75 MHz, Chloroform-*d*, 298 K, ppm) δ 192.4, 166.1, 145.5, 138.8, 137.9, 135.5, 131.5, 131.2, 130.4, 129.3, 128.9, 128.8, 128.6, 127.4, 127.0, 67.8.**HRMS (MALDI-FT ICR):** *m/z* calcd for $C_{21}H_{16}O_3$ $[M+Na]^+$= 339.0991, found: 339.1027.

General procedure for the synthesis of the α-amido sulfones derivatives 1a-1i[84].

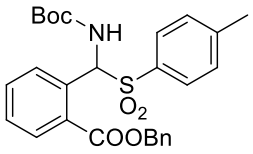
[84] Tillman, A. L.; Ye, J.; Dixon. D. J., *Chem. Commun.* **2006**, 1191-1193.



R= Bn, Me
R_1= H, Cl, Br, F
OMe,I, Ph
Pg= Boc,Cbz

1a (R_1=H; R=Bn; Pg= Boc)
1b (R_1=H; R=Bn; Pg=Cbz)
1c (R_1=F; R=Bn; Pg=Boc)
1d (R_1=Cl; R=Bn; Pg=Boc)
1e (R_1=Br; R=Bn; Pg=Boc)
1f (R_1=OMe; R=Bn; Pg=Cbz)
1g (R_1=I; R=Bn; Pg=Cbz)
1h (R_1=Ph; R=Bn; Pg=Cbz)
1i (R_1=H; R=Me; Pg= Boc)

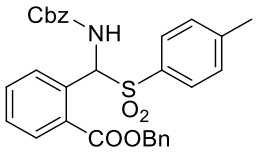
To a rapidly stirred suspension of tbutyl-carbamate (257 mg, 1.0 equiv, 2.2 mmol) and p-toluenesulfinic acid sodium salt (563 mg, 1.3 equiv, 2.9 mmol) in methanol/water (2:1, 2.5 mL/1.25 mL) were added benzyl 2-formylbenzoate a (528 mg, 1.0 equiv, 2.2 mmol) and formic acid (210 μL) at room temperature. The reaction mixture was vigorously stirred for three days and then filtered. The resulting white solid was washed with water and ether and then dried in vacuo to yield the pure sulfone, which was then used without further purification.



1a

Benzyl-2-(((tert-butoxycarbonyl)amino)(tosyl)methyl)-benzoate **(1a).**

Following the general procedure, the title compound was obtained as white solid in a 92% yield (1.00 g). Mp 124−126 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 6.9 Hz, 1H), 7.81 (d, J = 8.6 Hz, 2H), 7.65−7.50 (m, 5H), 7.48−7.30 (m, 5H), 6.22 (d, J = 10.4 Hz, 1H), 5.67 (d, J = 10.4 Hz, 1H), 5.41 (s, 2H), 2.41 (s, 3H), 1.27 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.1, 153.8, 145.0, 135.9, 134.4, 132.7, 132.6, 131.6, 131.4, 130.9, 129.9, 129.5, 129.4, 128.9, 128.8, 128.6, 81.1, 69.8, 67.5, 28.2, 21.9. HRMS (ESI-FT ICR) m/z calcd for $C_{27}H_{29}NO_6S$ $[M + K]^+$ 534.1353, found 534.1334.



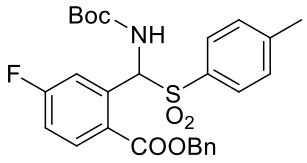
1b

Benzyl-2-((((benzyloxy)carbonyl)amino)(tosyl)methyl)-benzoate (**1b**).

Following the general procedure using 0.83 mmol a and benzyl-carbamate (1.0 equiv, 0.83 mmol), the title compound was obtained as a white solid in an 80% yield (350 mg).

Mp 124−126 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, J = 7.1 Hz, 1H), 7.72 (d, J = 8.1 Hz, 2H), 7.60−7.33 (m, 12H), 7.25−7.20 (m, 3H), 6.57 (d, J = 11.1 Hz, 1H), 5.40 (s, 2H), 4.96 (q, J = 11.7 Hz, 2H), 2.41 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 167.1, 154.9, 145.1, 135.9, 135.8, 134.2, 132.7, 131.5, 130.9, 129.8,

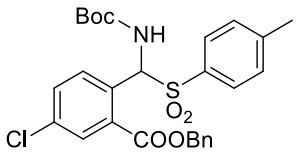
129.6, 129.3, 128.8, 128.6, 28.6, 128.5, 128.4, 70.6, 67.6, 21.9. HRMS (ESI-FT ICR) m/z calcd for $C_{30}H_{27}NO_6S$ $[M + K]^+$ 568.1196, found 568.1185.



1c

Benzyl-2-(((tert-butoxycarbonyl)amino)(tosyl)methyl)-4-fluorobenzoate (**1c**). Following the general procedure using 0.90 mmol c, the title compound was obtained as a white solid in a 94% yield (430 mg).

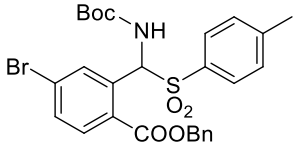
Mp 144−146 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14−8.10 (m, 1H), 7.83−7.75 (m, 3H), 7.48 (d, J = 6.9 Hz, 2H), 7.42−7.32 (m, 5H), 7.17−7.12 (m, 1H), 6.03 (d, J = 10.6 Hz, 1H), 5.40 (s, 2H), 2.42 (s, 3H), 1.27 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.0, 153.7, 145.2, 135.8, 135.3, 134.3, 134.0, 133.9, 129.9, 129.4, 128.8, 128.6, 128.5, 127.0, 116.5, 116.3, 81.3, 69.2, 67.5, 28.1, 21.8. HRMS (ESI-FT ICR) m/z calcd for $C_{27}H_{28}FNO_6S$ $[M + Na]^+$ 536.1519, found 536.1505.



1d

Benzyl-2-(((tert-butoxycarbonyl)amino)(tosyl)methyl)-5- chlorobenzoate (**1d**). Following the general procedure using 1.0 mmol d, the title compound was obtained as a white solid in a 72% yield (378 mg).

Mp 136−138 °C. ^{1}H NMR: (300 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.78 (d, J = 6.6 Hz, 2H), 7.56−7.48 (m, 2H), 7.44−7.31 (m, 7H), 6.12−6.08 (m, 1H), 5.41 (s, 2H), 2.42 (s, 3H), 1.26 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.9, 153.7, 145.2, 135.9, 135.5, 134.2, 132.6, 132.4, 131.3, 130.6, 130.2, 129.9, 129.4, 128.8, 128.7, 128.6, 81.3, 69.4, 67.8, 28.1, 21.8. HRMS (ESI-FT ICR) m/z calcd for $C_{27}H_{28}ClNO_6S$ $[M + Na]^+$ 552.1224, found 552.1223.



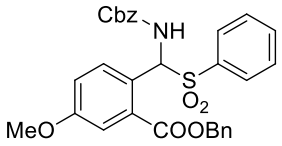
1e

Benzyl-4-bromo-2-(((tert-butoxycarbonyl)amino)(tosyl)-methyl)benzoate (**1e**). Following the general procedure using 1.6 mmol e, the title compound was obtained a white solid in a 72% yield

(660 mg).

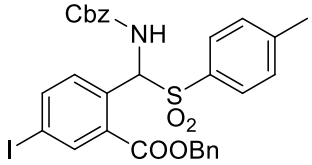
Mp 141−143 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 9.0 Hz, 1H), 7.81 (d, J = 7.5 Hz, 2H), 7.70−7.66 (m, 2H), 7.60 (d, J = 9.0 Hz, 1H), 7.48−7.32 (m, 6H), 6.05 (d, J = 10.5 Hz, 1H), 5.40 (s, 2H), 2.42 (s, 3H),

1.27 (s, 9H). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 166.3, 153.7, 145.3, 135.5, 134.2, 133.8, 132.6, 132.3, 129.9, 129.7, 129.4, 128.8, 128.6, 128.6, 127.5, 81.3, 69.1, 67.6, 28.1, 21.8. HRMS (ESI-FT ICR) m/z calcd for $C_{27}H_{28}BrNO_6S$ $[M + Na]^+$ 596.0718, found 596.0722.



1f

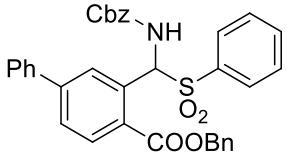
Benzyl-2-((((benzyloxy)carbonyl)amino)(phenylsulfonyl)-methyl)-5-methoxybenzoate (**1f**). Following the general procedure using 0.90 mmol f and benzyl-carbamate (1.0 equiv, 0.90 mmol), the title compound was obtained in a 67% yield (320 mg). The title compound slowly decomposed in solution at rt, therefore the 13C NMR spectrum was not recorded. Decomposition was also observed during the MS analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.69 (m, 2H), 7.57 (s, 1H), 7.47−7.33 (m, 8H), 7.26−7.20 (m, 4H), 7.07(s, 2H), 6.57 (d, J = 8.8 Hz, 1 H), 5.39 (s, 2H), 4.95 (q, J = 13.4 Hz, 2 H), 3.84 (s, 3H), 2.40 (s, 3H).



1g

Benzyl-2-((((benzyloxy)carbonyl)amino)(tosyl)methyl)-5-iodobenzoate (**1g**). Following the general procedure using 0.50 mmol g and benzyl-carbamate (1.0 equiv, 0.50 mmol), the title compound was obtained a white solid in a 61% yield (200 mg).

Mp 143−145 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.90 (d, J= 8.0 Hz, 1H), 7.70 (d, J = 8.0 Hz, 2H), 7.55−7.29 (m, 9H), 7.26−7.20 (m, 4H), 6.46 (d, J = 10.7 Hz, 1H), 5.40 (s, 2H), 4.95 (q, J =12.0 Hz, 2H), 2.41 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 165.7, 154.7, 145.4, 141.6, 140.0, 135.8, 135.5, 134.0, 132.5, 131.2, 130.7, 129.9, 129.3, 129.0, 128.9, 128.8, 128.7, 128.5, 128.4, 127.5, 95.7, 70.2, 67.7, 22.0. HRMS (ESI-FT ICR) m/z calcd for $C_{30}H_{26}INO_6S$ $[M + Na]^+$ 678.0423, found 678.0422.

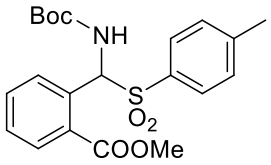


1h

Benzyl-3-((((benzyloxy)carbonyl)amino)(phenylsulfonyl)-methyl)-[1,1′-biphenyl]-4-carboxylate (**1h**). Following the general procedure using 0.32 mmol h and benzyl-carbamate (1.0 equiv, 0.32 mmol), the title compound was obtained in a 60% yield (114 mg).

The title compound slowly decomposed in solution at rt, therefore the ^{13}C NMR spectrum was not recorded. Decomposition was also observed during the MS analysis. ^{1}H NMR (300 MHz, CDC_{l3}) δ 8.14 (d, J = 7.6

Hz, 2 H), 7.77.-7.64 (m, 6H), 7.57 (d, J = 7.6 Hz, 3H), 7.49−7.33 (m, 9H), 7.21 (d, J = 8.3 Hz, 2H), 6.68 (d, J = 11.4 Hz, 1H), 5.43 (s, 2H), 4.96 (q, J = 12.5 Hz, 2H), 2.41 (s, 3H).

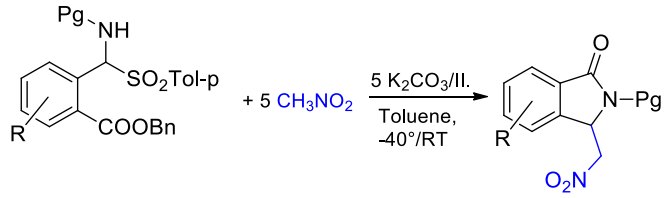


1i

Methyl-2-(((tert-butoxycarbonyl)amino)(tosyl)methyl)- benzoate (**1i**). Following the general procedure using 4.2 mmol methyl 2-formylbenzoate, the title compound was obtained as a white solid in a 92% yield (1.6 g).

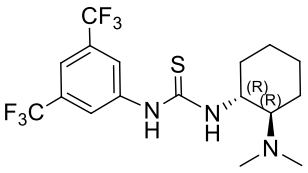
Mp 156−158 °C. ^{1}H NMR (400 MHz,$CDCl_3$) δ 8.04 (d, J = 6.5 Hz, 1H), 7.85 (d, J = 7.8 Hz, 2H), 7.60−7.49 (m, 4H), 7.34 (d, J = 7.8 Hz, 2H), 6.25 (d, J = 10.4 Hz, 1H), 5.73 (d, J = 10.4 Hz, 1H), 3.96 (s, 3H), 2.42 (s, 3H), 1.26 (s, 9H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 167.7, 153.8, 145.1, 132.5, 131.3, 131.0, 129.8, 129.4, 81.0, 69.9, 52.8, 28.1, 21.8. HRMS (ESI-FT ICR) m/z calcd for $C_{21}H_{25}NO_6S$ [M + Na]$^{+}$ 442.1300, found 442.1288.

Typical Procedure for the Asymmetric Synthesis of N-Carbamoyl-3-substituted Isoindolin-1-ones 3a−3h.



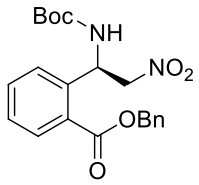
1a (R=H; Pg= Boc)
1b (R=H; Pg=Cbz)
1c (R=F; Pg=Boc)
1d (R=Cl; Pg=Boc)
1e (R=Br; Pg=Boc)
*1f (R=OMe; Pg=Cbz)
1g (R=I; Pg=Cbz)
*1h (R=Ph; Pg=Cbz)

3a (R=H; Pg= Boc)
3b (R=H; Pg=Cbz)
3c (R=F; Pg=Boc)
3d (R=Cl; Pg=Boc)
3e (R=Br; Pg=Boc)
3f (R=OMe; Pg=Cbz)
3g (R=I; Pg=Cbz)
3h (R=Ph; Pg=Cbz)



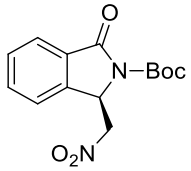
II

In an ACE tube, α-amido sulfones **1a−1i** (1 equiv, 0.08 mmol,), K_2CO_3 (55 mg, 5 equiv, 4 mmol), nitromethane (21 μL, 5 equiv, 0.4 mmol), and organocatalyst **II** (20 mol %) were stirred in at −40 °C in toluene (0.4 mL) until the starting material was completely converted to the intermediate. Then, the reaction mixture was allowed to slowly warm to room temperature, and stirring was continued until the intermediate disappeared (48 h). The mixture was directly purified by flash chromatography on silica gel.



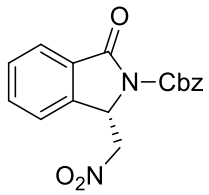
2a

(R)-Benzyl-2-(1-((tert-butoxycarbonyl)amino)-2-nitroethyl)benzoate (**2a**). Starting from 0.08 mmol α-amido sulfone **1a**, the compound was obtained as a very viscous oil (27 mg, 85%) after the direct purification on silica gel of the product from step 1 of the general reaction (hexane/ethyl acetate 5:1). $[\alpha]_D^{18}$= +2.3 (c = 0.40, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, J = 7.7 Hz, 1H), 7.55−7.36 (m, 8H), 6.13−6.07 (m, 2H), 5.38 (s, 2H), 4.93−4.78 (m, 2H), 1.41 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.2, 154.9, 139.3, 135.5, 133.5, 132.1, 129.3, 128.9, 128.7, 128.5, 128.2, 127.1, 80.5, 78.8, 67.5, 51.7, 28.4. HRMS (MALDI-FT ICR) m/z calcd for $C_{21}H_{24}N_2O_6$ $[M + Na]^+$ 423.1526, found 423.1542. HPLC analysis: Chiralpak OD-H column, n-hexane/i-PrOH 70:30, 0.8 mL/min, tR = 7.2 min, tS = 8.2 min. 96% ee.



3a

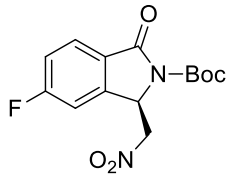
(R)-tert-Butyl-1-(nitromethyl)-3-oxoisoindoline-2-carboxylate (**3a**). Following the general procedure using 0.08 mmol α-amido sulfone 1a, the title compound was obtained as a very viscous oil in an 85% yield (20 mg) after chromatography on silica gel (hexane/ethyl acetate 5:1). $[\alpha]_D^{18}$= +31.3 (c = 0.75, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, J = 7.7 Hz, 1H), 7.70 (t, J = 7.8 Hz, 1H), 7.58 (t, J= 7.5 Hz, 1H), 7.48 (d, J = 8.1 Hz, 1H), 5.65 (dd, J1 = 6.0 Hz, J2 = 3.8 Hz,, 1H), 5.10 (dd, J_1 = 12.0 Hz, J_2 = 3.8 Hz, 1H), 4.77 (dd, J_1 = 12.0 Hz, J_2 = 6.3 Hz, 1H), 1.61 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, CDCl3) δ 165.4, 150.2, 140.9, 134.6, 131.0, 130.2, 125.7, 122.9, 84.9, 76.5, 57.1, 28.2. IR (neat) 1783, 1747, 1699, 1562, 1333, 756 cm−1. HRMS (MALDI-FT ICR) m/z calcd for $C_{14}H_{16}N_2O_5$ $[M + K]^+$ 331.0691, found 331,0710. HPLC analysis: Chiralpak OD-H column, n-hexane/i-PrOH 70:30, 0.8 mL/min, t_s = 13.4 min, t_r= 21.0 min. 96% ee. The reaction was also scaled to 1.0 mmol (495 mg) 1a under the same conditions, yielding 78% 3a (228 mg, 96% ee).



3b

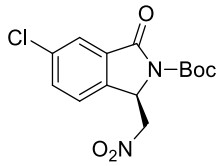
(S)-Benzyl-1-(nitromethyl)-3-oxoisoindoline-2-carboxylate (**3b**). Following the general procedure using 0.08 mmol α-amido sulfone 1b, the title compound was obtained as a very viscous oil in a 78% yield (20 mg) after chromatography on silica gel (hexane/ethyl acetate 5:1). $[\alpha]_D^{18}$= −32.8 (c = 0.75, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 7.4 Hz, 1H), 7.70 (t, J = 7.4 Hz, 1H), 7.59 (t, J= 7.4 Hz,

1H), 7.49 (s, 3H), 7.41−7.34 (m, 3H), 5.67 (m, 1H), 5.42 (s, 2H), 5.12 (d, J = 9.0 Hz, 1H), 4.84 (d, J = 9.0 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, CDCl3) δ 165.1, 151.8, 140.9, 135.0, 134.8, 130.4, 130.3, 128.9, 128.8, 128.3, 125.9, 123.0, 76.0, 69.0, 57.2. IR (neat) 1740, 1654, 1546, 1290, 788 cm−1. HRMS (MALDI-FT ICR) m/z calcd for $C_{17}H_{14}N_2O_5$ $[M + K]^+$ 365.0534, found 365.0520. HPLC analysis: Chiralpak IC column, n-hexane/i-PrOH 70:30, 1 mL/min, t_r = 27.8 min, t_s = 29.9 min. 92% ee.



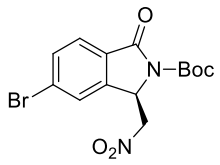
3c

(R)-tert-Butyl-5-fluoro-3-(nitromethyl)-1-oxoisoindoline-2-carboxylate (**3c**). Following the general procedure using 0.08 mmol α-amido sulfone 1c, the title compound was obtained as a very viscous oil in a 58% yield (14 mg) after chromatography on silica gel (hexane/ethyl acetate 5:1). $[\alpha]_D^{18}$= +66.9 (c = 0.35, $CHCl_3$). ^1H NMR: (400 MHz, $CDCl_3$) δ 7.94−7.90 (m, 1H), 7.29−7.27 (m, 1H), 7.19 (d, J = 7.5 Hz, 1H) 5.61 (m, 1H), 5.10 (d, J = 10.2 Hz, 1H), 4.80 (d, J = 10.0 Hz, 1H), 1.61 (s, 9H). ^{19}F NMR (400 MHz, chloroform-d, 298 K, ppm) δ −101.4. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 166.7 (JC−F = 259.1 Hz), 164.2, 150.0, 143.4 (JC−F = 9.9 Hz), 128.1 (JC−F =9.9 Hz), 126.8, 118.4 (JC−F = 19.9 Hz), 110.6 (JC−F = 29.9 Hz), 85.1, 76.1, 56.6, 28.2. IR (neat) 1770, 1605, 1564, 1551, 756 cm−1. HRMS (ESI-FT ICR) m/z calcd for $C_{14}H_{15}FN_2O_5$ $[M + Na]^+$ 333.0863, found 333.0856. HPLC analysis: Chiralpak OD-H column, n-hexane/ i-PrOH 70:30, 0.8 mL/min, t_s = 13.4 min, t_r = 21.4 min. 96% ee.



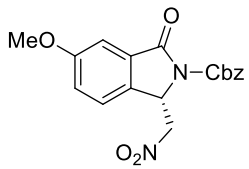
3d

(R)-tert-Butyl-5-chloro-1-(nitromethyl)-3-oxoisoindoline-2-carboxylate (**3d**). Following the general procedure using 0.08 mmol α-amido sulfone 1d, the title compound was obtained as a very viscous oil in an 81% yield (21 mg) after chromatography on silica gel (hexane/ethyl acetate 5:1). $[\alpha]_D^{18}$= +46.3 (c = 0.55, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.64 (d, J = 8.1 Hz, 1H), 7.43 (d, J= 8.1 Hz, 1H), 5.60−5.59 (m, 1H), 5.10 (dd, J_1 = 12.0 Hz, J_2 = 3.8 Hz, 1H), 4.80 (dd, J_1 = 12.0 Hz, J_2 = 6.0 Hz, 1H), 1.61 (s, 9H). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 164.0, 150.0, 139.0, 136.8, 134.7, 132.5, 125.6, 124.3, 85.3, 76.1, 56.8, 28.2. IR (neat) 1772, 1561, 1351, 761 cm−1. HRMS (MALDI-FT ICR) m/z calcd for $C_{14}H_{15}ClN_2O_5$ $[M + Na]^+$ 351.0537, found 351.0519. HPLC analysis: Chiralpak OD-H column, n-hexane/i-PrOH 70:30, 0.8 mL/min, t_s = 14.8 min, t_r = 18.9 min. 96% ee.



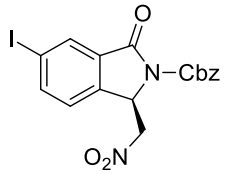
3e

(R)-tert-Butyl-5-bromo-3-(nitromethyl)-1-oxoisoindoline-2-carboxylate (**3e**). Following the general procedure using 0.08 mmol α-amido sulfone 1e, the title compound was obtained as a very viscous oil in a 67% yield (20 mg) after chromatography on silica gel (hexane/ethyl acetate 5:1). $[\alpha]_D^{18}$= +32.8 (c = 0.70, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76−7.67 (m, 3H); 5.60 (m, 1H), 5.08 (d, J =12.0 Hz, 1H), 4.81 (dd, J_1 = 12.0 Hz, J_2 = 6.2 Hz, 1H), 1.60 (s, 9H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 164.4, 150.0, 142.6, 133.9, 129.7, 129.6, 127.0, 126.4, 85.2, 76.0, 56.6, 28.8. IR (neat) 1745, 1712, 1546, 1330, 745 cm−1. HRMS (ESI-FT ICR) m/z calcd for $C_{14}H_{15}BrN_2O_5$ $[M + Na]^+$ 393.0062, found 393.0053. HPLC analysis: Chiralpak OD-H column, n-hexane/i-PrOH 70:30, 0.8 mL/min, t_s = 14.7 min, t_r = 21.9 min. 98% ee.



3f

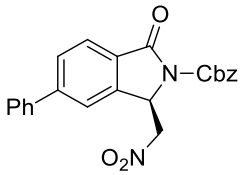
(S)-Benzyl-5-methoxy-1-(nitromethyl)-3-oxoisoindoline-2-carboxylate (**3f**). Following the general procedure using 0.08 mmol α-amido sulfone 1f, the title compound was obtained as a very viscous oil in a 64% yield (18 mg) after chromatography on silica gel (hexane/ethyl acetate 5:1). $[\alpha]_D^{18}$= −40.3 (c = 0.40, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, J = 7.1 Hz, 2H), 7.43−7.35 (m, 5H), 7.24 (dd, J_1 = 2.3 Hz, J_2 = 6.4 Hz, 1H), 5.6 (dd, J_1 = 6.3 Hz, J_2 = 3.8 Hz, 1H), 5.42 (s, 2H), 5.09 (dd, J1 = 12.0 Hz, J2 = 3.7 Hz, 1H), 4.77 (dd, J1 = 12.1 Hz, J2 = 6.3 Hz, 1H), 3.87 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.2, 161.5, 151.7, 135.0, 133.0, 131.8, 128.9, 128.8, 128.3, 124.0, 123.4, 107.9, 76.2, 68.9, 56.8, 56.0. IR (neat) 1726, 1710, 1551, 1499, 1343, 781 cm−1. HRMS (ESI-FT ICR) m/z calcd for $C_{18}H_{16}N_2O_6$ $[M + Na]^+$ 379.0906, found 379.0895. HPLC analysis: Chiralpak OD-H column, n-hexane/i-PrOH 60:40, 1 mL/ min, t_s = 20.4 min, t_r = 30.6 min. 88% ee.



3g

(R)-Benzyl-5-iodo-1-(nitromethyl)-3-oxoisoindoline-2-carboxylate (3g). Following the general procedure using 0.08 mmol α-amido sulfone 1g, the title compound was obtained as a very viscous oil in a 58% yield (21 mg) after chromatography on silica gel (hexane/ethyl acetate 5:1). $[\alpha]_D^{18}$= +11.8 (c = 0.80, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 8.00 (d, J = 7.1 Hz, 1H), 7.48 (d, J= 7.1 Hz, 1H), 7.40−7.37 (m, 4H), 7.24 (s, 1H), 5.60 (m, 1H), 5.41(bs, 2H), 5.09 (d, J = 11.9 Hz, 1H), 4.81 (dd, J_1 = 12.5

Hz, J_2 = 6.0 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, CDCl3) δ 163.4, 151.5, 143.6, 140.1, 134.9, 134.8, 132.3, 128.9, 128.9, 128.4, 124.7, 95.7, 75.5, 69.2, 57.0. IR (neat) 1745, 1555, 1381, 1118, 775 cm−1. HRMS (ESI-FT ICR) m/z calcd for $C_{17}H_{13}IN_2O_5$ $[M + Na]^+$ 474.9767, found 474.9759. HPLC analysis: Chiralpak AS-H column, n-hexane/i-PrOH 80:20, 0.8 mL/min, t_s = 66.2 min, t_r = 71.1 min. 90% ee.

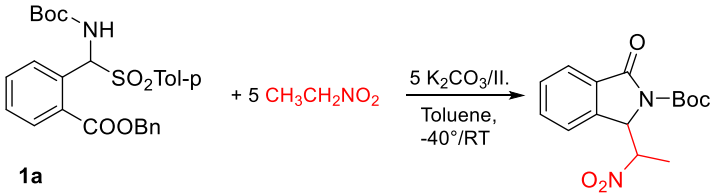


3h

(R)-Benzyl-3-(nitromethyl)-1-oxo-5-phenylisoindoline-2-carboxylate (**3h**). Following the general procedure using 0.08 mmol α-amido sulfone 1h, the title compound was obtained as a very viscous oil in an 83% yield (26 mg) after chromatography on

silica gel (hexane/ethyl acetate 5:1). $[\alpha]_D^{18}$= +12.4 (c = 0.40, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, J = 8.3 Hz, 1H), 7.79 (d, J = 8.3 Hz,1H), 7.64−7.57 (m, 3H), 7.52−7.35 (m, 8H), 5.72 (dd, J1 = 6.5 Hz, J2 = 3.6 Hz, 1H), 5.43 (s, 2H), 5.17 (dd, J_1 = 12.5 Hz, J_2 = 3.8 Hz, 1H), 4.85 (dd, J1 = 12.0 Hz, J2 = 6.6 Hz, 1H). 13C{1H} NMR (150 MHz, CDCl3) δ 164.8, 151.7, 148.2, 141.5, 139.3, 134.9, 129.5, 129.2, 128.9, 128.7, 128.6, 128.2, 127.6, 126.1, 121.4, 75.9, 68.9, 57.0. IR (neat) 1765, 1699, 1674, 1533, 1302, 781 cm−1. HRMS (ESI-FT ICR) m/z calcd for $C_{23}H_{18}N_2O_5$ $[M + K]^+$ 441.0847, found 441.0859. HPLC analysis: Chiralpak IC column, n-hexane/i-PrOH 60:40, 1 mL/min, t_s = 24.6 min, t_r = 30.1 min. 84% ee.

tert-Butyl-1-(1-nitroethyl)-3-oxoisoindoline-2-carboxylate(4).



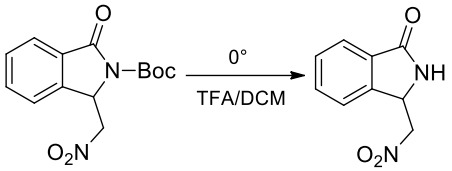
1a **4**

In an ACE tube, α-amido sulfone **1a** (27 mg, 1 equiv, 0.08 mmol), K_2CO_3 (55 mg, 5 equiv, 0.4 mmol), nitroethane (28 µL, 5 equiv, 0.4 mmol), and organocatalyst **II** (20 mol %) were stirred in at −40 C° in toluene (0.4 mL) until the starting material was completely converted to the intermediate. Then, the reaction mixture was allowed to slowly warm to room temperature, and the stirring was continued until the intermediate disappeared (96 h). The crude was directly purified by flash chromatography on silica gel (hexane/ethyl acetate 7:3).

Yield: 14 mg, 54% (solid). dr: 72/28. ^1H NMR mixture of diastereomers (400 MHz, $CDCl_3$) δ 7.93 (d, J = 7.3 Hz, 1H, major diastereomer), 7.72−7.67 (m, 1H, major diastereomer), 7.59−7.55 (m, 2H, major diastereomer), 5.89 (bs, 1H, minor diastereomer), 5.77 (bs, 1H, major diastereomer), 5.50−5.49 (m, 1H,

minor diastereomer), 5.05−5.04 (m, 1H, major diastereomer), 1.62 (s, 9H, minor diastereomer), 1.57 (s, 9H, major diastereomer), 1.42 (d, J = 6.4 Hz, 3H, major diastereomer), 1.06 (d, J = 6.4 Hz, 3H, minor diastereomer). $^{13}C\{^{1}H\}$ NMR mixture of diastereomers (100 MHz, $CDCl_3$) δ 165.9 (×2), 150.1 (×2), 140.7, 139.3, 134.5, 134.4, 131.0, 130.2, 125.8, 125.6, 123.9, 122.9, 85.1, 84.8, 83.3, 81.0, 62.0, 60.7, 28.3, 28.0, 12.3, 11.1. HRMS (ESI-FT ICR) m/z calcd for $C_{15}H_{18}N_2O_5$ $[M + K]^+$ 345.0847, found 345.0852. HPLC analysis: Chiralpak OD-H column, n-hexane/i-PrOH 80:20, 0.8 mL/min, tminor,d_1= 8.3 min, $t_2$major,d_1= 8.8 min, tminor,d2= 17.1 min, $t_2$major,d_2= 18.9 min. 85% ee_1 and 40% ee_2.

(R)-3-(Nitromethyl)isoindolin-1-one (5).



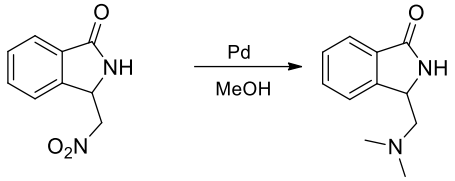
3a **5**

In a round bottom flask, **3a** (20 mg, 1 equiv, 0.07 mmol) was stirred in CH_2Cl_2 (300 μL) and CF_3COOH (150 μL) for 10−15 min at 0 °C. The mixture was diluted with DCM and water. To the mixture was added 1 M NaOH at rt under stirring until the pH reached 7, then the aqueous phase was further extracted twice with DCM. The combined organic layers were dried over Na_2SO_4, filtered and evaporated in vacuo. The crude mixture was purified by flash chromatography on

silica gel (hexane/ethyl acetate 1:1).

Yield: 14 mg, 99% (white solid). Mp 142−144 °C. $[\alpha]_D^{18}$= −31.6 (c = 0.15, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, J = 7.7 Hz, 1H), 7.65−7.58 (m, 2H), 7.45 (d, J = 7.7 Hz, 1H), 6.97 (s, 1H), 5.28 (d, J = 10.3 Hz, 1H), 4.91 (dd, J_1 = 12.3, J_2 = 3.1 Hz, 1H), 4.38 (dd, J_1 = 12.3, J_2 = 10.2 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (75 MHz, DMSO-d_6) δ 170.0, 143.4, 133.1, 132.4, 129.5, 124.1, 123.7, 78.2, 54.2. IR (KBr) 3180, 1718, 1546 cm−1. HRMS (ESI-FT ICR) m/z calcd for $C_9H_8N_2O_3$ $[M + Na]^+$ 215.0427, found 215.0424. HPLC analysis: Chiralpak OD-H column, n-hexane/i-PrOH 80:20, 0.6 mL/min, t_r = 35.2 min, t_s = 40.1 min. 96% ee.

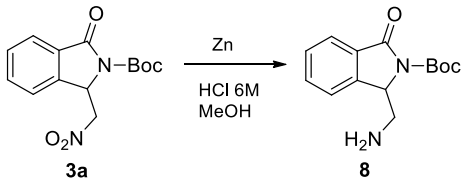
(R)-3-((Dimethylamino)methyl)isoindolin-1-one (7).



5 **7**

A suspension of **5** (12 mg, 1 equiv, 0.06 mmol) and 10% Pd/C (20 mol%) in methanol (1 mL) was stirred under a hydrogen atmosphere for 18 h at room temperature. The mixture was filtered on Celite and eluted with MeOH/DCM. The organic layer was then evaporated under reduced pressure, and the crude product was purified by flash chromatography on silica (chloroform/methanol 95:5). Yield: 6 mg, 53% (very viscous oil). $[\alpha]_D^{18}$= −54.7 (c = 0.30, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, J = 7.2 Hz, 1H), 7.57−7.42 (m, 3H), 6.76 (s, 1H), 4.65 (dd, J_1 = 11.1 Hz, J_2 = 3.5 Hz, 1H), 2.67 (dd, J_1 = 12.0 Hz, J_2 = 3.8 Hz, 1H), 2.36 (m, 6 + 1H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 170.5, 145.7, 132.4, 131.9, 128.6, 124.2, 122.7, 64.4, 54.8, 45.9 (2C, −NMe2). IR (neat) 2787, 1695, 1468, 1303, 748 cm−1. HRMS (MALDI-FT ICR) m/z calcd for $C_{11}H_{14}N_2O$ $[M + Na]^+$ 213.0998, found 213.0996. HPLC analysis: Chiralpak IC column, n-hexane/i-PrOH 60:40, 1 mL/min, t_s = 11.0 min, t_r = 11.9 min. 80% ee.

(R)-tert-Butyl-1-(aminomethyl)-3-oxoisoindoline-2-carboxylate (8).



3a **8**

To a solution of compound **3a** (20 mg, 1 equiv, 0.07 mmol,) in methanol (500 μL) in a round-bottom flask were added zinc dust (23 mg, 4 equiv, 0.3 mmol) and 6 M HCl (90 μL) at 0 °C. The mixture was stirred at room temperature for 40−45 min. Then, the mixture was basified with 1 M NaOH until the pH reached 7 and extracted twice with ethyl acetate. Combined organic layers were then dried over Na_2SO_4 and evaporated in vacuo. Purification by flash chromatography on silica gel (chloroform/methanol 95:5) gave the product. Yield: 11 mg, 61% (very viscous oil). $[\alpha]_D^{18}$= +15.1 (c = 0.40, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 7.5 Hz, 1H), 7.66 (t, J = 7.5 Hz, 1H), 7.52−7.51 (m, 2H), 5.09 (bs, 1H), 3.50−
3.46 (m, 1H), 3.31 (m, 1H), 1.61 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.3, 150.5, 143.5, 134.1, 131.7, 129.1, 125.3, 122.7, 83.7, 62.2, 44.1, 28.3. IR (neat) 2979, 2933, 1772, 1708, 1335, 1151 cm−1. HRMS (MALDI-FT ICR) m/z calcd for $C_{14}H_{18}N_2O_3$ $[M + Na]^+$ 285.1209, found 285.1200. HPLC analysis: Chiralpak OD-H column, n-hexane/i-PrOH 80:20, 0.8 mL/min, t_r = 10.1 min, t_s = 11.9 min. 96% ee.

Crystallographic data

Crystals of compound **3e** suitable for single crystal X-ray diffraction analysis were obtained dissolving 14 mgof the compound in a mixture of chloroform (0.3 mL) and hexane (0.1 mL) at room temperature. After the complete dissolution, the saturated solution was cooled down to -18°C. Crystals were obtained after few days. For the measurement, a colourless prismatic crystal of 0.34 mm x 0.21 mm x 0.07 mm was selected andmounted on a cryoloop with paratone oil.

Data collection was performed at room temperature with a Bruker D8 QUEST diffractometer equipped witha PHOTON II detector using Cu*Kα* radiation (λ= 1.54178 Å).

Data indexing, integration and reduction were performed using *CrysAlisPro* ver. 1.171.41.122a.[9] Empirical absorption correction was performed with *CrysAlisPro* ver. 1.171.41.122a using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm. The structure was solved using SHELXS-97[10] and refinedthrough full matrix least-squares based on F[10] using the program SHELXL.[11]

Non-hydrogen atoms were refined anisotropically, hydrogen atoms were positioned geometrically and included in structure factors calculations but not refined.

The chirality on carbon atom C2 (R) was successfully assigned by anomalous-dispersion effects in diffractionmeasurements on the crystal (Flack parameter -0.025(14)).

ORTEP diagrams (Figure S1) was drawn using *OLEX2*. In Table S1 are reported the crystallographic data.

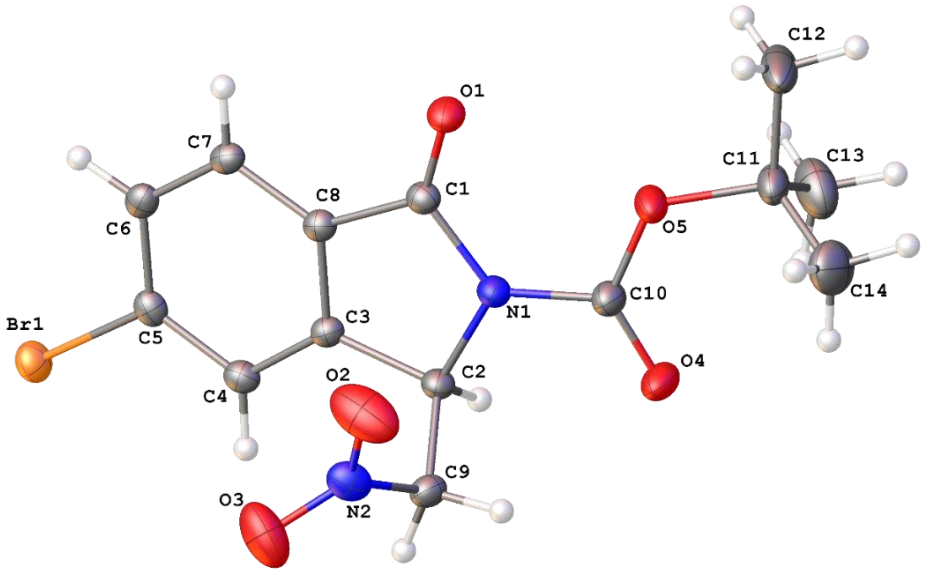


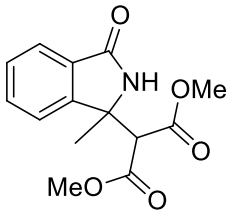
Figure S1. ORTEP drawings for compound **3e**. Atom types: C grey, H white, Br orange, O red, N blue.

Ellipsoids are drawn at 20% probability level. CCDC 2143635 contains the supplementary crystallographic data, which can be accessed available free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

Table S1. Crystallographic data for compound **3e**.

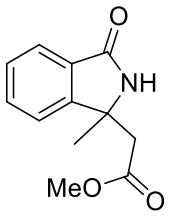
	3e
T (K)	296
Formula	$C_{14}H_{15}BrN_2O_5$
Formula weight	371.18
System	Orthorhombic
Space group	$P2_12_12_1$
***a* (Å)**	6.50468(9)
***b* (Å)**	7.19264(8)
***c* (Å)**	33.7877(4)
***α* (°)**	90
***β* (°)**	90
***γ* (°)**	90
***V* (Å^3)**	1580.79(3)
Z	4
***D*$_x$ (g cm^{-3})**	1.560
λ (Å)	1.54178
***μ* (mm^{-1})**	3.779
***F*$_{000}$**	752.0
R1 (I > 2σI)	0.0379(2719)
$_wR_2$	0.1024(2861)
N. of param.	203
GooF	1.069
Flack parameter	-0.025(14)
***ρ*$_{min}$, *ρ*$_{max}$ (eÅ^3)**	-0.51, 0.40

5.4 isoindolinones of pharmaceutical interest: general procedures and spectroscopic data



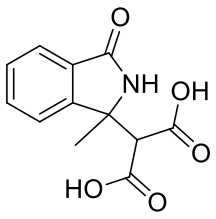
7 *Dimethyl 2-(1-Methyl-3-Oxoisoindolin-1-yl) Malonate (**7**)*

To a solution of 2-acetylbenzonitrile **6** (500 mg, 3.44 mmol, 1.0 eq.) in dry CH_3CN (1.2 mL), potassium carbonate (476 mg, 3.44 mmol, 1.0 eq.) and dimethylmalonate (1.5 mL, 10 mmol, 3.0 eq.) were added. The mixture was stirred at 50 °C for 24 h, then diluted with chloroform and filtered. Purification by crystallization (Dichloromethane/Hexane, 5 mL/12.5 mL) at −20 °C for 24 h afforded the pure product, as a yellow solid. Yield: 85% (809 mg). HRMS (ESI) *m/z:* [M + H]+ calcd. for $C_{14}H_{16}NO_5$ 278.10230; found: 278.10280. ^{1}H NMR (300 MHz, CDCl3): δ 7.80 (d, *J* = 7.38 Hz, 1H), 7.58–7.50 (m, 1H), 7.46 (t, *J* = 7.50 Hz, 1H), 7.38 (d, *J* = 7.59 Hz, 1H), 7.20 (brs, 1H), 3.84 (s, 1H), 3.79 (s, 3H), 3.43 (s, 3H), 1.68 (s, 3H).



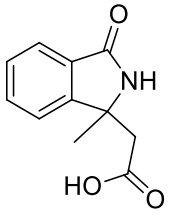
8 *Methyl 2-(1-Methyl-3-Oxoisoindolin-1-yl) Acetate (**8**)*

In a Schlenk tube, anhydrous lithium chloride (180 mg, 4.0 eq.) was added to a solution of dimethyl 2-(1-methyl-3-oxoisoindolin-1-yl) malonate **7** (300 mg, 1.10 mmol, 1.0 eq.) in DMSO (5.0 mL) and water (500 μL). The reaction mixture was stirred at 130 °C until the starting material disappeared by thin-layer chromatography ($CHCl_3$/AcOEt,1:4). The reaction mixture was diluted with ethyl acetate and washed with brine, and then the organic phase was dried on anhydrous sodium sulphate and concentrated under reduced pressure to give an oil. Purification by flash chromatography on silica gel (Hexane/AcOEt 50/50) gave the pure product as a yellow wax-type oil. Yield: 70% (240 mg). IR (KBr): 3201, 1720, 1680 cm−1. HRMS (ESI) *m/z:* [M + H]+ calcd for $C_{12}H_{14}NO_3$ 220.09682, found: 220.09679. ^{1}H NMR (400 MHz, $CDCl_3$): 7.83 (d, *J* = 7.53 Hz, 1H), 7.57 (t, *J* = 7.39 Hz, 1H), 7.47 (t, *J* = 7.49 Hz, 1H), 7.37 (d, *J* = 7.56 Hz, 1H), 7.14 (bs, 1H), 3.72 (s, 3H), 2.96 (d, *J* = 16.3 Hz, 1H), 2.51 (d, *J* = 16.3 Hz, 1H), 1.59 (s, 3H).



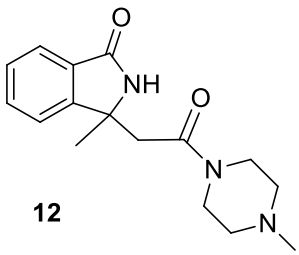
9 *2-(1-Methyl-3-Oxoisoindolin-1-yl) Malonic Acid (**9**)*

Isoindolinone **7** (400 mg, 1.44 mmol) was dissolved in CH_2Cl_2 (12 mL, 0.12M), and 2M NaOH in MeOH (6.5 mL) was added with stirring of the mixture at room temperature for 24 h. The solvent was removed under reduced pressure, and then the white solid was solubilized in water (2.5 mL) and washed with ethyl acetate. The aqueous layer was then acidified with 3N HCl and extracted with ethyl acetate 5 times, giving a white foam. Yield: 97% (350 mg). Used in the next reaction without further purification. IR (KBR): 3520, 1720, 1706, 1701 cm−1. HRMS (MALDI) *m/z:* [M + H]+ calcd for $C_{12}H_{12}NO_5$ 250.07100, found: 250.07179. 1H NMR (CD OD, 250 MHz): δ 7.74–7.52 (m, 3H), 7.50 (t, *J* = 8.15 Hz, 1H), 4.02 (s, 1H) 1.70 (s, 3H). 13C-NMR (CD3OD, 62.5 MHz): δ 170.7, 169.7, 168.7, 150.4, 132.3, 131.1, 129.1, 128.3, 122.6, 61.3, 29.8, 24.1.



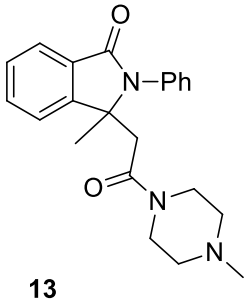
10 *2-(1-Methyl-3-Oxoisoindolin-1-yl) Acetic Acid (**10**)*

Compound **9** (300 mg, 1.20 mmol) was solubilized in CH_3CN (5.2 mL, 0.23 M) and refluxed overnight. The solvent as removed under reduced pressure and rinsed with chloroform twice, affording a slightly yellow waxy oil. Yield: 99% (250 mg). IR (KBR): 3504, 1724, 1702 cm−1. HRMS (MALDI) *m/z:* [M + H]+ calcd for $C_{11}H_{12}NO_3$ 206.08117, found: 206.08089. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 11.33 (br s, 1H, COOH), 8.79 (s, 1H, NH) 7.82 (d, *J* = 7.17 Hz, 1H), 7.59 (t, *J* = 7.23 Hz, 1H), 7.49–7.41 (m, 2H), 3.07 (d, *J* = 16.38 Hz, 1H), 2.53 (d, *J* = 16.38 Hz, 1H), 1.69 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 174.5, 171.0, 151.8, 132.8, 130.3, 128.8, 124.4, 121.3, 60.3, 44.1, 24.7.



12 *3-Methyl-3-(2-(4-Methylpiperazin-1-yl) -2-Oxoethyl) Isoindolin-1-One (**12**)*

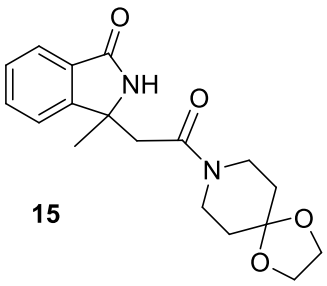
To a solution of compound **10** (0.24 mmol, 1.0 eq.) in CH_2Cl_2 (2.8 mL), Et3N (0.48 mmol, 2.0 eq.), EDC.HCl (0.24 mmol, 1.0 eq.) and HOBt (0.24 mmol, 1.0 eq.), amine **11** (0.28 mmol, 1.2 eq.) was added, and the reaction mixture was allowed to stir at room temperature for 24 h. The mixture was diluted with dichloromethane and a small amount of K2CO3 was added. Purification by chromatography on silica gel ($CHCl_3$/MeOH, 95:5) gave the product as an oil. Yield: 84% (58 mg). IR (neat): 3200, 1742, 1720, 1599 cm−1. HRMS (MALDI) *m/z:* $[M + H]^+$ calcd. for $C_{16}H_{22}N_3O_2$ 288.17065, found: 288.17083. 1H NMR ($CDCl_3$, 300 MHz): δ 7.83 (d, *J* = 7.42 Hz, 1H), 7.55 (t, *J* = 7.54 Hz, 1H), 7.47–7.43 (m, 2H), 7.37 (d, *J* = 7.42 Hz, 1H), 3.78–3.76 (m, 1H), 3.75–3.74 (m, 1H), 3.55–3.38 (m, 2H), 2.98 (d, *J* = 16.38 Hz, 1H), 2.48–2.22 (m + s, 8H), 1.65 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 168.8, 168.5, 152.4, 132.1, 131.2, 128.5, 124.4, 121.1, 59.6, 55.0, 54.8, 46.1, 45.5, 42.4, 41.6, 25.2.



13 *3-Methyl-3-(2-(4-Methylpiperazin-1-yl)Acetyl)-2-Phenylisoindolin-1-One (**13**)*

Amide arylation was carried out according to a literature procedure[85]. A mixture of isoindolinone **12** (0.134 mmol), iodobenzene (0.268 mmol), CuI (0.0268 mmol) and K_2CO_3 (0.134 mmol) was dissolved in DMF (300 μL), evacuated and backfilled with nitrogen and then stirred under a nitrogen atmosphere at 140 °C for 36 h. The resulting palebrown suspension was cooled to room temperature, diluted with NH3 and extracted twice with ethyl acetate. Purification by chromatography on silica gel ($CHCl_3$/MeOH, 90:10) gave the product as brown solid. Yield: 81% (39 mg). Mp. 162 °C (dec.). IR (KBr): 1743, 1718, 1600 cm−1. HRMS (MALDI) *m/z* $[M + H]^+$ calcd. for $C_{22}H_{26}N_3O_2$ 364.20195, found: 364.20107. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.92 (d, *J* = 7.31 Hz, 1H), 7.56–7.40 (m, 6H), 7.31–7.26 (m, 2H), 3.52 (t, *J* = 4.69 Hz, 2H), 3.24–3.13 (m, 1H), 3.09–3.01 (m, 1H), 2.75 (app q, *J* = 14.4 Hz, 2H), 2.30–2.28 (m, 3H), 2.23 (s, 3H), 2.10–2.07 (m, 1H), 1.73 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 168.2, 167.2, 149.5, 135.8, 132.1, 131.4, 129.8, 129.7, 128.5, 124.3, 122.1, 65.7, 54.6, 54.5, 45.9, 45.7, 41.3, 40.5, 26.4.

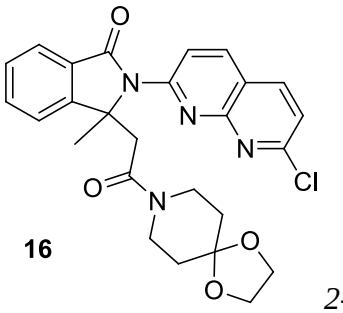
[85] Sughara, M.; Ukita, T.,*Chem. Pharm. Bull.* **1997**, *45*, 719–721.



15

*3-Methyl-3-(2-oxo-2-(1,4-Dioxa-8-Azaspiro [4.5] Decan-8-yl) Ethyl) Isoindolin-1-One (**15**)*

To a solution of compound **10** (0.24 mmol, 1.0 eq) in CH_2Cl_2 (2.8 mL), Et_3N (0.48 mmol, 2.0 eq.) and DEPC (0.24 mmol, 1.0 eq.), amine **14** (0.28 mmol, 1.2 eq.) was added, and the reaction mixture was allowed to stir at room temperature for 24 h. The reaction mixture was quenched with 1N HCl (2 mL) and extracted with dichloromethane. The organic layer was dried over $MgSO_4$, evaporated in vacuo and then purified by chromatography on silica gel (Ethyl acetate/MeOH, 95:5) to give a white solid. Mp. 150–151 °C. Yield: 74% (59 mg). IR (KBr): 3203, 1747, 1720, 1600 cm−1. HRMS (MALDI) *m/z:* [M + Na]$^+$ calcd. for $C_{18}H_{22}N_2O_3Na$ 331.14718, found: 331.14957. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.83 (d, *J* = 7.41 Hz, 1H), 7.58–7.56 (m, 2H), 7.51–7.39 (m, 2H), 3.96 (s, 4H), 3.78–3.77 (m, 1H), 3.75–3.69 (m, 1H), 3.47–3.43 (m, 2H), 3.02 (d, *J* = 16.29 Hz, 1H), 2.36 (d, *J* = 16.29 Hz, 1H), 1.66–1.64 (m, 7H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.8, 168.3, 152.3, 132.2, 131.1, 128.5, 124.4, 121.1, 106.7, 64.6, 59.7, 43.6, 42.2, 39.9, 35.6, 34.8, 25.0.

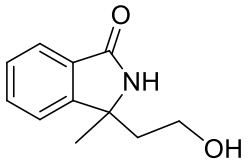


16

*2-(7-Chloro-1,8-Naphthyridin-2-yl)-3-Methyl-3-(2-oxo-2-(1,4-Dioxa-8-Azaspiro [4.5]Decan-8-yl) Ethyl) Isoindolin-1-One (3-Methyl-Pazinaclone, **16**)*

To a solution of isoindolinone **15** (60 mg, 0.18 mmol, 1.0 eq.) in 1,4-dioxane (1 mL), 9,9-dimethyl-4,5 bis(diphenylphosphino)xanthene (Xantphos) (12 mg, 10 mol%), 2,7-dichloro-1,8- naphthyridine (40 mg, 1.2 eq.), Pd (OAc)2 (5 mg, 10 mol%) and potassium carbonate (50 mg, 2.0 eq.) were evacuated and flushed with nitrogen. The mixture was stirred at 80 °C for 48 h. The mixture was allowed to cool and then partitioned between EtOAc and water. The organic extract was washed with brine, dried by $MgSO_4$ and evaporated in *vacuo*. Purification by chromatography ($CHCl_3$/MeOH, 98: 2) gave the product as white solid. Mp. 235–236 °C. Yield: 65% (58 mg). IR (neat): 1741, 1720, 1609, 1280 cm−1. HRMS (MALDI) *m/z:* [M + H]$^+$ calcd. for $C_{26}H_{26}ClN_4O_4$ 493.16371, found: 493.16117. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 9.02 (d, *J* = 9.37 Hz, 1H), 8.17 (d, *J* = 8.90 Hz, 1H), 8.10 (d, *J* = 8.37 Hz, 1H), 7.95 (d, *J* = 7.61

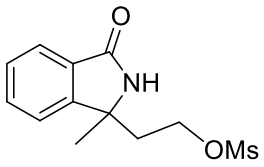
Hz, 1H), 7.67 (t, *J* = 7.37 Hz, 1H), 7.57–7.46 (m, 2H), 7.41 (d, *J* = 8.05 Hz, 1H), 4.48 (d, *J* = 15.35 Hz, 1H), 3.87 (s, 4H), 3.67–3.44 (m, 4H), 3.33 (d, *J* = 15.35 Hz, 1H), 2.08 (s, 3H), 1.80–1.54 (m, 4H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 169.9, 167.9, 155.7, 154.7, 154.4, 152.2, 139.6, 138.6, 134.7, 131.0, 128.9, 125.1, 122.6, 121.6, 119.4, 118.1, 107.5, 67.9, 64.9, 44.5, 40.2, 40.0, 36.1, 35.3, 30.4, 27.7.



17

*3-(2-Hydroxyethyl)-3-Methylisoindolin-1-One (**17**)*

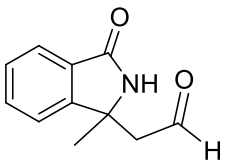
To a solution in anhydrous THF (4.80 mL) of compound **8** (210 mg, 0.96 mmol, 1.0 eq.), under nitrogen atmosphere in an ice bath, 2M $LiBH_4$ (784 µL, 1.5 eq.) was added dropwise, and the reaction mixture was allowed to stir at room temperature overnight. The mixture was diluted with water (5 mL), and the aqueous phase was extracted three times with AcOEt (20 mL), giving a pale oil. Yield: 99% (180 mg). IR (neat): 3501, 1720, 1600 cm−1. HRMS (MALDI) *m/z:* $[M + H]^+$ calcd. for $C_{11}H_{14}NO_2$ 192.1000; found: 192.10191. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.80 (d, *J* = 7.76 Hz, 1H), 7.55 (t, *J* = 7.71 Hz, 1H), 7.46–7.26 (m, 3H), 3.75–3.73 (m, 2H), 2.84 (br s, 1H, OH), 2.11–1.99 (m, 2H), 1.56 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.3, 125.7, 132.3, 131.0, 128.3, 124.0, 121.3, 61.5, 58.6, 41.7, 25.5.



18

*2-(1-Methyl-3-oxoisoindolin-1-yl)ethylmethanesulfonate (**18**)*

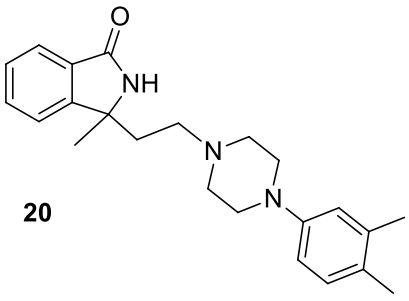
In anhydrous DCM (240 µL) to a solution of alcohol **17** (90 mg, 0.48 mmol, 1.0 eq.) under nitrogen atmosphere, triethylamine (100 µL, 0.71 mmol, 1.5 eq.) and methansulfonyl chloride (43 µL, 0.55 mmol, 1.2 eq.) were added. The reaction mixture was stirred for 2 h at room temperature. *Method A workup*. The solvent was removed under reduced pressure, and the crude was diluted with AcOEt and washed with water recovering a pale oil. Yield: 95% (133 mg). *Method B work up*. The crude was directly purified by chromatography on Florisil ($CHCl_3$/MeOH, 99:1). Yield: 73% (102 mg). IR (neat): 3471, 1720, 1400, 1201 cm−1. HRMS (ESI) *m/z:* $[M + Na]^+$ calcd. for $C_{12}H_{15}NO_4SNa$ 292.0614; found: 292.0614. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.82 (d, *J* = 7.67 Hz, 1H), 7.61- 7.59 (m, 2H), 7.51–7.49 (m, 1H), 7,42–7.40 (m, 1H), 4.09–3.99 (m, 2H), 2.83 (s, 3H), 2.42–2.33 (m, 2H), 1.61 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.2, 150.7, 132.7, 131.2, 128.8, 124.2, 121.5, 65.8, 60.4, 38.8, 37.3, 27.2.



19

*2-(1-Methyl-3-Oxoisoindolin-1-yl) Acetaldehyde (**19**)*

Alcohol (70 mg, 0.36 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (1.6 mL), Dess–Martin periodinane (186 mg, 0.44 mmol, 1.2 eq.) was added and the mixture was stirred for 2 h at room temperature. Then, the suspension was diluted with dichloromethane (3 mL) and washed with 1N NaOH (1 mL), giving a pale oil, and it was purified by chromatography on silica gel (Ethyl acetate/MeOH, 95:5). Yield: 99% (68 mg). IR (neat): 3501, 1720, 1605 cm−1. HRMS (MALDI) *m/z:* $[M + Na]^+$ calcd. for $C_{11}H_{11}NO_2Na$ 212.06820; found: 212.06764. ^1H NMR ($CDCl_3$, 300 MHz): δ 9.64 (s, 1H, CHO), 7.84 (d, *J* = 7.62 Hz, 1H), 7.60 (t, *J* = 7.31 Hz, 1H), 7.51–7.40 (m, 3H), 3.13 (d, *J* = 17.31 Hz, 1H), 2.74 (d, *J* = 17.58 Hz 1H), 1.64 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 199.8, 169.5, 151.1, 132.6, 130.8, 128.8, 124.4, 121.2, 59.1, 52.5, 25.9.



20

*3-(2-(4-(3,4-Dimethylphenyl) Piperazin-1-yl) Ethyl)-3-Methylisoindolin-1-One (3-Methyl-PD172938, **20**)*

Pathway A. A mixture of compound **18** (120 mg, 0.44 mmol, 1.0 eq.) in $CHCl_3$ (1.0 mL), triethylamine (60 µL, 0.44 mmol, 1.0 eq.) and 3,4 dimethylphenylpiperazine (100 mg, 0.53 mmol, 1.2 eq.) was stirred at 50 °C for 24 h. Purification by chromatography on silica gel ($CHCl_3$/MeOH, 99/1) gave the product as a pink solid. Yield: 80% (127 mg).

Pathway B. Aldehyde **19** (60 mg, 0.30 mmol, 1.0 eq.) was dissolved in MeOH (2.4 mL), 3,4 (dimethyl) phenylpiperazine (62 mg, 0.30 mmol, 1.0 eq) was added and the mixture was stirred at room temperature for 5 h. Then, $NaBH_4$ (32 mg, 1.5 eq.) was added and stirring was continued for 2 h. Purification by chromatography on silica gel ($CHCl_3$/MeOH, 99:1) gave the product as a pink solid. Yield: 80% (87 mg). Mp. 57–58 °C. IR (neat): 3205, 1720 cm−1. HRMS (MALDI) *m/z:* $[M + H]^+$ calcd. for $C_{23}H_{30}N_3O$ 364.23830, found: 364.23834. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.82 (d, *J* = 7.27 Hz, 1H, 7.56 (t, *J* = 7.48 Hz, 1H), 7.45 (t, *J* = 7.27 Hz, 1H), 7.37 (d, *J* = 7.27 Hz, 1H), 7.28 (s, 1H, NH), 7.00 (d, *J* = 7.75 Hz, 1H), 7.69 (m, 2H), 3.20 (m, 1H), 3.13 (s, 3H), 2.65 (m, 2H), 2.44 (m, 5H), 2.22 (s, 3H), 2.17 (s, 3H),

2.03 (m, 1H), 1.54 (s, 3H).^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.6, 152.5, 149.6, 137.2, 132.2, 131.3, 130.3, 128.4, 128.3, 124.2, 121.1, 118.4, 114.1, 61.2, 54.0, 53.5, 49.9, 36.4, 25.7, 20.3, 18.9.

Asymmetric Synthesis of (S)-PD172938 3-Methylated Analog, (S)-20 Dimethyl 2-(1-methyl-3-oxoisoindolin-1-yl)malonate *(S)*-7.

Prepared by a literaturemodified procedure. In a round bottom flask, 2-acetylbenzonitrile 6 (250 mg, 1.72 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (0.07M), then dimethylmalonate (750 μL, 5.16 mmol, 3 eq.), catalyst (*R,R*)-21 (107 mg, 10% mol) and K_3PO_4 (730 mg, 3.44 mmol, 2.0 eq.) were
added and the mixture was stirred at room temperature for 24 h. After filtration of the inorganic salt, the solvent was removed, and the crude was purified by chromatography on silica gel (Hexane/Ethyl acetate, 50:50) affording a white solid. Yield: 84% (400 mg). Ee: 44%, Chiracel OD-H Hex/*i*-PrOH 80/20, 0.6 mL/min, λ 254 nm, t_{minor}: 15.3 min and t_{major}: 16.7 min. Crystallization procedure*:* the sample was dissolved in a mixture of CH_2Cl_2/Hexane (12 mL, 1/4) at room temperature and then left at −20 °C for 72 h. The enantio-enriched product was recovered as waxy oil. ee: 94%. $[\alpha]_D^{21}$: −101.6 (c 0.3, $CHCl_3$). Yield: 47% (188 mg).

2-(1-Methyl-3-oxoisoindolin-1-yl) malonic acid *(S)*-8 and 2-(1-Methyl-3-oxoisoindolin-1-yl)acetic acid *(S)*-9. Prepared as reported for racemic compounds, starting from 180 mg (0.65 mmol) of enantioenriched compound *(S)*-7. Used without further purification. Yield after two steps: 99% (135 mg). The enantiomeric excess of the acid was determined after derivatization into methylester derivative *(S)*-8. Methyl 2-(1-methyl-3-oxoisoindolin-1-yl) acetate, *(S)*-8. Isoindolinone *(S)*-10 (135 mg, 0.64 mmol, 1.0 eq.) was dissolved in acetone (8.5 mL), then potassium carbonate (51 mg, 0.37 mmol, 0.6 eq.) and dimethylsulphate (110 μL, 1.10 mmol, 1.5 eq.) were added, keeping the reaction at 50 °C under stirring for 2 h. After filtration of inorganic salt, the crude was
purified by chromatography on silica gel (Hexane/Ethyl acetate 50:50) affording the ester as a pale oil. Yield: 98% (140 mg). ee: 94%. Chiracel IE-3 Hex/*i*-PrOH 70/30, 0.6 mL/min, λ 254 nm, $t_{minor:}$ 28.5 min and t_{major}: 35.9 min. $[\alpha]_D^{21}$: −66.1 (c 0.3, $CHCl_3$). Spectroscopic data are in agreement with racemate.

3-(2-Hydroxyethyl)-3-methylisoindolin-1-one *(S)*-17 and 2-(1-Methyl-3-oxoisoindolin-1-yl)ethylmethanesulfonate *(S)*-18 were prepared as described for racemic compounds, starting from 140 mg (0.64 mmol) of enantioenriched compound *(S)*-8 and used without further purification.

2-(1-Methyl-3-oxoisoindolin-1-yl)acetaldehyde *(S)*-19 were prepared as described for racemic compound, starting from 35 mg (0.18 mmol) of enantoenriched compound *(S)*-17. Purification by

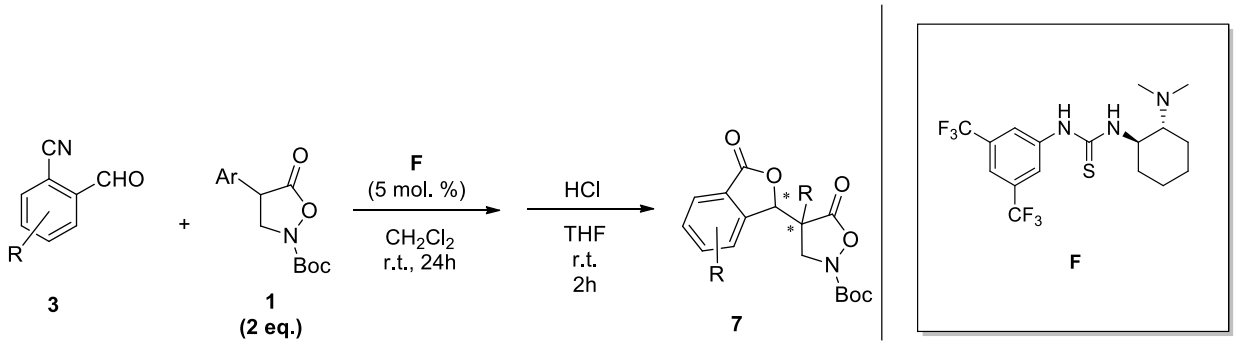
chromatography on silica gel (Ethyl acetate/MeOH 95:5) gave a pale oil. Yield: 99% (34 mg). $[\alpha]_D^{25}$: −52.4 (c 0.8, $CHCl_3$).

3-(2-(4-(3,4-Dimethylphenyl)piperazin-1-yl)ethyl)-3-methylisoindolin-1-one *(S)*-20.

Pathway A. (S)-18 (60 mg, 0.22 mmol, 1.0 eq.) was dissolved in $CHCl_3$ (350 μL), then trimethylamine (30 μL, 0.22 mmol, 1.0 eq.) and 3,4-(dimethyl) phenylpiperazine (50 mg, 0.53 mmol, 1.2 eq.) were added and the mixture was stirred at 50 °C for 24 h. Purification by chromatography on silica gel ($CHCl_3$/MeOH 99:1) gave the product as pink wax oil. Yield: 80% (63 mg). Ee: 94%. *Pathway B.* Aldehyde *(S)*-**19** (30 mg, 0.15 mmol, 1.0 eq.) was dissolved in MeOH (1.2 mL), 3,4-(dimethyl) phenylpiperazine (31 mg, 0.15 mmol, 1 eq.) was added and the mixture was stirred at room temperature for 5 h. Then, $NaBH_4$ (16 mg, 1.5 eq.) was added and stirring was continued for 2 h. Purification by chromatography on silica gel (CHCl3/MeOH 99:1) gave the product as pink wax oil. Yield: 80% (43 mg). ee: 94%. Chiracel OD-H Hex/*i*-PrOH 80/20, 0.6 mL/min, λ 254 nm, t_{minor}: 14.9 min and t_{major}: 24.3 min. HRMS (MALDI) *m/z:* $[M + H]^+$ calcd. for $C_{23}H_{30}N_3O$ 364.23835; found: 364.23834. $[\alpha]_D^{19}$: −25.0 (c 0.3, $CHCl_3$). Spectroscopic data were found in agreement with racemate, as reported above.

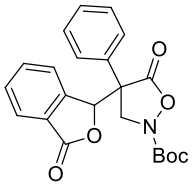
5.5 Phtalides hybrids: general procedures and spectroscopic data

Synthesis and Analytic Details of Targets 7, 8 and 9



General Procedure for the Cascade Reaction Forming Products 7

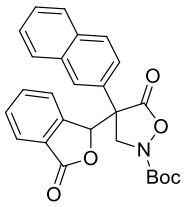
In a round bottom-flask, 2-cyanobenzaldehydes **3** (1 eq., 0.10 mmol) were added at room temperature to a stirred solution of isoxazolidin-5-ones **1** (2 eq., 0.20 mmol) and catalyst **F** (5% mol) in DCM (3mL). After stirring for 24 h, the mixture was purified directly by flash chromatography on silica gel with heptane:ethyl acetate = 6:4 to give the intermediates **6** as mixtures of diasteroisomers. These products were then dissolved in a solution of 0.5 M HCl (1 mL) and THF (3 mL). The mixture was stirred at room temperature for 2 h and then concentrated in vacuum. The resulting residue was treated with saturated $NaHCO_3$ (20 mL), extracted with CH_2Cl_2 (4x30 mL), and then purified by flash chromatography (heptane:EtOAc= 7:3).



7a

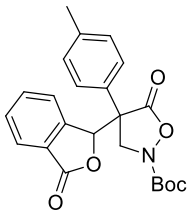
Following the general procedure using 0.1 mmol of the respective 2-cyanobenzaldehyde compound **7a** was obtained in 67% yield with *e.r.= 87:13* (83:17) *d.r.:* 70/30 as an oily residue (26 mg, 0.067 mmol).

$[\alpha]_D^{23}$ (c = 0.50, $CHCl_3$) = +47.3°.^{1}H NMR (300 MHz, δ, $CDCl_3$, 298 K): 7.77-7.75 (m, 1H), 7.49-7.43 (m, 4H), 7.34-7.31 (m, 3H), 7.06 (d, *J* = 7.1 Hz, 1H), 5.97 (s, 1H), 4.70 (d, *J* = 12.2, 1H), 4.17 (d, *J* = 12.2, 1H), 1.27 (s, 9H). ^{13}C NMR (75 MHz, δ, $CDCl_3$, 298 K): 173.0, 169.1, 155.7, 144.8, 134.1, 130.1, 129.9, 129.6, 127.4, 125.7, 124.2, 84.5, 81.0, 55.6, 54.2, 27.7. HRMS (ESI): calcd *m/z* for $C_{22}H_{21}NO_6$: 418.1267 $[M+Na]^+$; found: 418.1260. HPLC (YMC Chiral ART Amylose-SA, eluent: hexane:*i*-PrOH = 70:30, 0.6 mL/min, 10 °C), retention times: $t_{minor\ d1}$=12.6 min, $t_{major\ d1}$= 18.8 min, $t_{minor\ d2}$=16.4 min, $t_{major\ d2}$= 21.2 min.



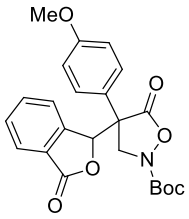
7b Following the general procedure using 0.1 mmol of the respective 2-cyanobenzaldehyde compound **7b** was obtained in 68% yield with *e.r.= 88:12* (85:15) *d.r.:* 70/30 as oily residue (30 mg, 0.068 mmol).

$[\alpha]_D^{23}$ (c = 1.00, $CHCl_3$) = +48.9°. ^{1}H NMR (300 MHz, δ, $CDCl_3$, 298 K): 7.85-7.67 (m, 4H), 7.52-7.43 (m, 4H), 7.36-7.33 (m, 2H), 6.96-6.93 (m, 1H), 6.03 (s, 1H), 4.75 (d, *J* = 12.2 Hz, 1H), 4.15 (d, *J* = 12.2 Hz, 1H), 1.11 (s, 9H). ^{13}C NMR (75 MHz, δ, $CDCl_3$, 298 K): 173.0, 169.1, 155.7, 144.8, 134.2, 134.2, 133.2, 133.2, 133.0, 132.8, 130.2, 130.1, 129.7, 129.3, 128.4, 128.4, 127.8, 127.7, 127.6, 127.5, 127.4, 127.3, 127.0, 126.7, 126.4, 126.0, 125.8, 124.2, 124.0, 123.9, 123.4, 84.5, 81.0, 55.8, 54.1, 27.6. HRMS (ESI): calcd *m/z* for $C_{26}H_{23}NO_6$: 468.1423 $[M+Na]^+$; found: 468.1416. HPLC (YMC Chiral ART Amylose-SA, eluent: hexane:*i*-PrOH = 70:30, 0.6 mL/min, 10 °C), retention times: $t_{minor\ d1}$=15.1 min, $t_{major\ d1}$= 23.7 min, $t_{minor\ d2}$=19.9 min, $t_{major\ d2}$= 36.0 min.



7d Following the general procedure using 0.1 mmol of the respective 2-cyanobenzaldehyde compound **7d** was obtained in 62% yield with *e.r.= 87:13* (77:23) *d.r.:* 75/25 as an oily residue (25 mg, 0.062 mmol).

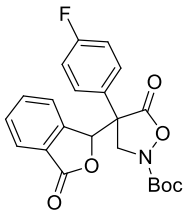
$[\alpha]_D^{23}$ (c = 1.00, $CHCl_3$) = +36.3°.^{1}H NMR (300 MHz, δ, $CDCl_3$, 298 K): 7.79-7.76 (m, 1H), 7.49-7.45 (m, 2H), 7.35.7.32 (m, 3H), 7.14 (d, *J* = 7.8 Hz, 2H), 5.96 (s, 1H), 4.64 (d, *J* = 12.2 Hz, 1H), 4.09 (d, *J* = 12.2 Hz, 1H), 2.30 (s, 3H), 1.29 (s, 9H). ^{13}C NMR (75 MHz, δ, $CDCl_3$, 298 K): 173.0, 169.1, 155.7, 144.9, 144.7, 139.8, 139.7, 134.1, 130.2, 129.9, 127.6, 127.2, 126.8, 126.7, 126.4, 125.9, 125.7, 124.2, 123.4, 84.4, 81.1, 57.5, 56.2, 55.3, 53.8, 27.7, 27.6, 21.0. HRMS (ESI): calcd *m/z* for $C_{23}H_{23}NO_6$: 432.1423 $[M+Na]^+$; found: 432.1417. HPLC (YMC Chiral ART Amylose-SA, eluent: hexane:*i*-PrOH = 70:30, 0.6 mL/min, 10 °C), retention times: $t_{minor\ d1}$=12.3 min, $t_{major\ d1}$= 18.5 min, $t_{minor\ d2}$=14.8 min, $t_{major\ d2}$= 23.5 min.



7e

Following the general procedure with additional 5 mol% K_2CO_3 using 0.1 mmol of the respective 2-cyanobenzaldehyde compound **7e** was obtained in 36% yield with *e.r.= 77:23* (71:29) *d.r.:* 75/25 as an oily residue (15 mg, 0.035 mmol).

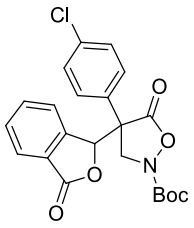
$[\alpha]_D^{23}$ (c = 0.30, $CHCl_3$) = +30.6°. ^{1}H NMR (300 MHz, δ, $CDCl_3$, 298 K): 7.81-7.78 (m, 1H), 7.52-7.47 (m, 2H), 7.40-7.37 (m, 2H), 7.07-7.02 (m, 1H), 6.86 (d, *J* = 9.3 Hz, 2H), 5.96 (s, 1H), 4.64 (d, *J* = 12.1 Hz, 1H), 4.11 (d, *J* = 12.1 Hz, 1H), 3.78 (s, 3H), 1.32 (s, 9H). ^{13}C NMR (75 MHz, δ, $CDCl_3$, 298 K): 173.1, 169.1, 144.9, 134.1, 130.0, 129.0, 128.7, 126.5, 125.9, 124.7, 124.2, 123.4, 121.5, 114.8, 114.5, 84.4, 81.1, 55.4, 54.9, 53.9, 27.7. HRMS (ESI): calcd *m/z* for $C_{23}H_{23}NO_7$: 448.1372 $[M+Na]^+$; found: 448.1367. HPLC (YMC Chiral ART Amylose-SA, eluent: hexane:*i*-PrOH = 70:30, 1 mL/min, 10 °C), retention times: $t_{minor\ d1}$=9.5 min, $t_{major\ d1}$= 16.7 min, $t_{minor\ d2}$=11.7 min, $t_{major\ d2}$= 21.5 min.



7f

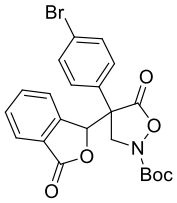
Following the general procedure using 0.1 mmol of the respective 2-cyanobenzaldehyde compound **7f** was obtained in 49% yield with *e.r.= 91:9* (85:15) *d.r.:* 80/20 as an oily residue (20 mg, 0.049 mmol).

$[\alpha]_D^{23}$ (c = 1.00, $CHCl_3$) = +58.4°. ^{1}H NMR (300 MHz, δ, $CDCl_3$, 298 K): 7.76 (d, *J* = 7.0 Hz, 1H), 7.56-7.39 (m, 5H), 7.23-7.18 (m, 1H), 7.03-6.97 (m, 2H), 5.93 (s, 1H), 4.68 (d, *J* = 12.2 Hz, 1H), 4.25 (d, *J* = 12.2 Hz, 1H), 1.30 (s, 9H). ^{13}C NMR (75 MHz, δ, $CDCl_3$, 298 K): 172.8, 168.9, 155.6, 144.6, 134.5, 134.2, 130.4, 130.2, 129.8, 129.7, 129.5, 129.4, 126.4, 125.8, 125.8, 124.2, 123.3, 116.7, 116.4, 116.1, 84.7, 80.8, 56.7, 56.0, 55.2, 55.0, 27.7. HRMS (ESI): calcd *m/z* for $C_{22}H_{20}FNO_6$: 436.1172 $[M+Na]^+$; found: 436.1169. HPLC (YMC Chiral ART Amylose-SA, eluent: hexane:*i*-PrOH = 70:30, 0.6 mL/min, 10 °C), retention times: $t_{minor\ d1}$=14.0 min, $t_{major\ d1}$= 19.5 min, $t_{minor\ d2}$=16.2 min, $t_{major\ d2}$= 28.3 min.



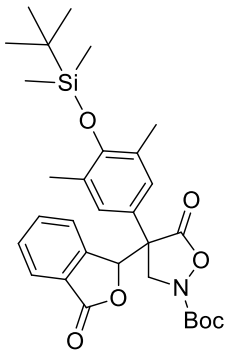
7g Following the general procedure using 0.1 mmol of the respective 2-cyanobenzaldehyde compound **7g** was obtained in 48% yield with *e.r.= 89:11* (87:13*) d.r.:* 80/20 as an oily residue (21 mg, 0.048 mmol).

$[\alpha]_D^{23}$ (c = 1.00, $CHCl_3$) = +28.2°. ^{1}H NMR (300 MHz, δ, $CDCl_3$, 298 K): 7.78 (d, *J* = 7.3 Hz, 1H), 7.58-7.49 (m, 3H), 7.39-7.28 (m, 4H), 5.94 (s, 1H), 4.67 (d, *J* = 12.2 Hz, 1H), 4.26 (d, *J* = 12.2 Hz, 1H), 1.32 (s, 9H). ^{13}C NMR (75 MHz, δ, $CDCl_3$, 298 K): 172.6, 168.9, 155.6, 144.5, 135.9, 134.3, 130.3, 129.7, 129.3, 129.1, 128.9, 128.6, 126.4, 125.9, 124.2, 84.8, 80.7, 55.3, 27.7. HRMS (ESI): calcd *m/z* for $C_{22}H_{20}ClNO_6$: 452.0877 $[M+Na]^+$; found: 452.0873. HPLC (YMC Chiral ART Amylose-SA, eluent: hexane:*i*-PrOH = 70:30, 0.6 mL/min, 10 °C), retention times: $t_{minor\ d1}$=14.8 min, $t_{major\ d1}$= 20.3 min, $t_{minor\ d2}$=17.5 min, $t_{major\ d2}$= 30.8 min.



7h Following the general procedure using 0.1 mmol of the respective 2-cyanobenzaldehyde compound **7h** was obtained in 68% yield with *e.r.= 90:10* (87:13) *d.r.:* 80/20 as an oily residue (32 mg, 0.067 mmol).

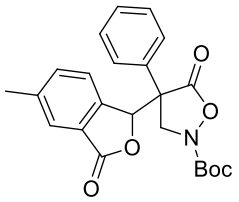
$[\alpha]_D^{23}$ (c = 1.00, $CHCl_3$) = +28.1°.^{1}H NMR (500 MHz, δ, $CDCl_3$, 298 K): 7.77 (d, *J* = 7.3 Hz, 1H), 7.55-7.42 (m, 4H), 7.30 (d, *J* = 8.2 Hz, 2H), 7.24 (d, *J* = 7.3 Hz, 1H), 5.93 (s, 1H), 4.65 (d, *J* = 12.3 Hz, 1H), 4.24 (d, *J* = 12.3 Hz, 1H), 1.31 (s, 9H). ^{13}C NMR (125 MHz, δ, $CDCl_3$, 298 K): 172.9, 169.2, 155.9, 144.8, 134.9, 134.7, 133.0, 132.7, 130.8, 130.6, 129.7, 129.5, 126.7, 126.5, 126.2, 124.5, 124.4, 123.6, 85.2, 81.5, 80.9, 56.8, 55.7, 55.1, 28.0. HRMS (ESI): calcd *m/z* for $C_{22}H_{20}BrNO_6$: 496.0372 $[M+Na]^+$; found: 496.0365. HPLC (YMC Chiral ART Amylose-SA, eluent: hexane:*i*-PrOH = 70:30, 0.6 mL/min, 10 °C), retention times: $t_{minor\ d1}$=11.9 min, $t_{major\ d1}$= 16.3 min, $t_{minor\ d2}$=14.6 min, $t_{major\ d2}$= 25.3 min.



7i

Following the general procedure using 0.1 mmol of the respective 2-cyanobenzaldehyde compound **7i** was obtained in 58% yield with *e.r.= 85:15* (65:35) *d.r.:* 75/25 as an oily residue (32 mg, 0.058 mmol).

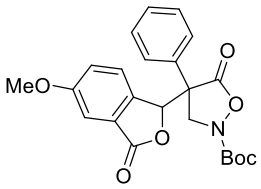
$[\alpha]_D^{23}$ (c = 1.00, $CHCl_3$) = +123.4°. ^{1}H NMR (300 MHz, δ, $CDCl_3$, 298 K): 7.79-7.76 (m, 1H), 7.46-7.43 (m, 2H), 7.03 (m, 2H), 6.88-6.86 (m, 1H), 5.94 (s, 1H), 4.57 (d, *J* = 12.2 Hz, 1H), 3.98 (d, *J* = 12.2 Hz, 1H), 2.14 (s, 6H), 1.30 (s, 9H), 0.97 (s, 9H), 0.14 (s, 3H), 0.12 (s, 3H). ^{13}C NMR (350 MHz, δ, $CDCl_3$, 298 K): 173.3, 169.3, 156.0, 153.5, 145.2, 134.0, 130.1, 129.8, 128.0, 127.8, 126.6, 125.8, 124.4, 122.0, 84.3, 81.2, 54.9, 53.1, 32.0, 29.2, 27.9, 26.2, 22.8, 18.9, 18.1, 14.3. HRMS (ESI): calcd *m/z* for $C_{30}H_{39}NO_7Si$: 576.2393 $[M+Na]^+$; found: 576.2388. HPLC (YMC Chiral ART Amylose-SA, eluent: hexane:*i*-PrOH = 90:10, 0.6 mL/min, 10 °C), retention times: $t_{minor\ d1}$=15.7 min, $t_{major\ d1}$= 21.7 min, $t_{minor\ d2}$=19.2 min, $t_{major\ d2}$= 33.8 min.



7j

Following the general procedure using 0.1 mmol of the respective 2-cyanobenzaldehyde compound **7j** was obtained in 51% yield with *e.r.= 91:9* (88:12) *d.r.:* 75/25 as an oily residue (21 mg, 0.051 mmol).

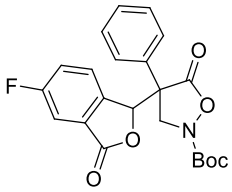
$[\alpha]_D^{23}$ (c = 0.80, $CHCl_3$) = +39.5°. ^{1}H NMR (300 MHz, δ, $CDCl_3$, 298 K): 7.56 (s, 1H), 7.49-7.44 (m, 3H), 7.35-7.33 (m, 3H), 7.85 (d, *J* = 7.8 Hz, 1H), 5.93 (s, 1H), 4.67 (d, *J* = 11.9 Hz, 1H), 4.12 (d, *J* = 11.9 Hz, 1H), 2.37 (s, 3H), 1.28 (s, 9H). ^{13}C NMR (75 MHz, δ, $CDCl_3$, 298 K): 173.0. 169.2, 155.7, 142.1, 140.5, 135.4, 135.3, 130.1, 129.6, 129.5, 129.5, 129.2, 127.7, 127.4, 126.6, 126.0, 125.7, 123.8, 123.0, 84.5, 81.0, 55.6, 53.8, 27.7, 21.2. HRMS (ESI): calcd *m/z* for $C_{23}H_{23}NO_6$: 432.1423 $[M+Na]^+$; found: 432.1418. HPLC (YMC Chiral ART Amylose-SA, eluent: hexane:*i*-PrOH = 70:30, 0.6 mL/min, 10 °C), retention times: $t_{minor\ d1}$=11.8 min, $t_{major\ d1}$= 16.9 min, $t_{minor\ d2}$=15.0 min, $t_{major\ d2}$= 18.7 min



7k

Following the general procedure using 0.1 mmol of the respective 2-cyanobenzaldehyde compound **7k** was obtained in 36% yield with *e.r.= 91:9* (91:9) *d.r.:* 85/15 as an oily residue (15 mg, 0.036 mmol).

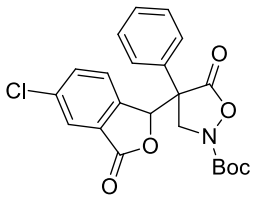
$[\alpha]_D^{23}$ (c = 0.30, $CHCl_3$) = +138.0°. ^{1}H NMR (300 MHz, δ, $CDCl_3$, 298 K): 7.49-7.45 (m, 3H), 7.35 (t, *J* = 3.2 Hz, 3H), 7.19 (d, *J = 2.5 Hz*, 1H), 6.90 (d, *J* = 8.5 Hz, 1H), 5.92 (s, 1H), 4.70 (d, *J* = 12.4 Hz, 1H), 4.15 (d, *J* = 12.4 Hz, 1H), 3.81 (s, 3H), 1.29 (s, 9H). ^{13}C NMR (75 MHz, δ, $CDCl_3$, 298 K): 173.0, 169.1, 161.2, 155.7, 137.0, 136.7, 133.3, 130.1, 129.6, 129.5, 129.2, 128.2, 128.0, 127.9, 127.6, 127.4, 125.1, 124.2, 122.9, 122.9, 107.5, 84.5, 81.0, 55.8, 55.7, 55.6, 53.9, 27.7. HRMS (ESI): calcd *m/z* for $C_{23}H_{23}NO_7$: 448.1372 $[M+Na]^+$; found: 448.1369. HPLC (YMC Chiral ART Amylose-SA, eluent: hexane:*i*-PrOH = 70:30, 0.6 mL/min, 10 °C), retention times: $t_{minor\ d1}$=13.6 min, $t_{major\ d1}$= 19.2 min, $t_{minor\ d2}$=15.9 min, $t_{major\ d2}$= 22.2 min.



7l

Following the general procedure using 0.1 mmol of the respective 2-cyanobenzaldehyde compound **7l** was obtained in 66% yield with *e.r.= 85:15* (75:25) *d.r.:* 70/30 as an oily residue (27 mg, 0.065 mmol).

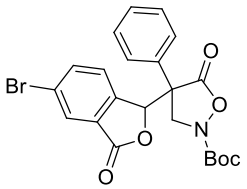
$[\alpha]_D^{23}$ (c = 1.00, $CHCl_3$) = +71.7°.^{1}H NMR (300 MHz, δ, $CDCl_3$, 298 K): 7.51-7.49 (m, 2H), 7.42-7.37 (m, 3H), 7.33-7.32 (m, 3H), 7.24-7.21 (m, 1H), 5.94 (s, 1H), 4.79 (d, *J* = 12.3 Hz, 1H), 4.26 (d, *J* = 12.3 Hz, 1H), 1.27 (s, 9H). ^{13}C NMR (75 MHz, δ, $CDCl_3$, 298 K): 173.1, 167.8 (*J* = 3.9 Hz), 165.1, 161.8, 155.6, 140.4 (*J* = 2.3 Hz), 129.7 (*J* = 9.2 Hz), 129.3, 128.6 (*J* = 9.2 Hz), 127.3, 126.3 (*J* = 8.2 Hz), 122.0 *(J* = 23.3 Hz*)*, 112.0 (*J* = 23.3 Hz), 84.6, 81.0, 55.7, 55.2, 27.6. HRMS (ESI): calcd *m/z* for $C_{22}H_{20}FNO_6$: 436.1172 $[M+Na]^+$; found: 436.1169. HPLC (YMC Chiral ART Amylose-SA, eluent: hexane:*i*-PrOH = 90:10, 1 mL/min, 10 °C), retention times: $t_{minor\ d1}$=13.8 min, $t_{major\ d1}$= 25.5 min, $t_{minor\ d2}$=18.2 min, $t_{major\ d2}$= 33.6 min



7m

Following the general procedure using 0.1 mmol of the respective 2-cyanobenzaldehyde compound **7m** was obtained in 69% yield with *e.r.= 85:15* (77:23) *d.r.:* 70/30 as an oily residue (29 mg, 0.069 mmol).

$[\alpha]_D^{23}$ (c = 1.00, $CHCl_3$) = +31.8°.^{1}H NMR (300 MHz, δ, $CDCl_3$, 298 K): 7.70 (d, *J* = 1.7 Hz, 1H), 7.49-7.39 (m, 3H), 7.34-7.32 (m, 3H), 7.19 (d, *J* = 8.1 Hz, 1H), 5.93 (s, 1H), 4.79 (d, *J* = 12.5 Hz, 1H), 4.26 (d, *J* = 12.5 Hz, 1H), 1.27 (s, 9H). ^{13}C NMR (75 MHz, δ, $CDCl_3$, 298 K): 173.1, 167.6, 155.6, 143.0, 136.5, 134.4, 129.7, 129.7, 129.3, 128.2, 127.3, 125.7, 125.5, 84.6, 81.0, 55.6, 55.2, 27.6. HRMS (ESI): calcd *m/z* for $C_{22}H_{20}ClNO_6$: 452.0877 $[M+Na]^+$; found: 452.0874. HPLC (YMC Chiral ART Amylose-SA, eluent: hexane:*i*-PrOH = 90:10, 1 mL/min, 10 °C), retention times: $t_{minor\ d1}$=13.6 min, $t_{major\ d1}$= 25.3 min, $t_{minor\ d2}$=17.1 min, $t_{major\ d2}$= 32.1 min.

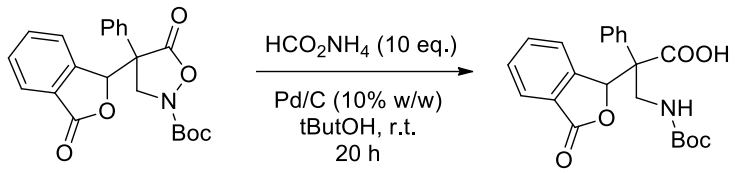


7n

Following the general procedure with additional 5 mol K_2CO_3 using 0.1 mmol of the respective 2-cyanobenzaldehyde compound **7n** was obtained in 30% yield with *e.r.= 90:10* (78:22) *d.r.:* 75/25 as an oily residue (14 mg, 0.03 mmol).

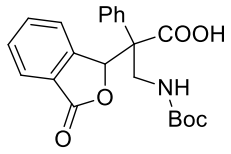
$[\alpha]_D^{23}$ (c = 0.80, $CHCl_3$) = +41.6°.^{1}H NMR (400 MHz, δ, $CDCl_3$, 298 K): 7.86 (d, *J* = 1.7 Hz, 1H), 7.61 (dd, J^1 = 1.7 Hz, J^2 = 6.4 Hz, 1H), 7.39-7.38 (m, 2H), 7.33-7.31 (m, 3H), 7.11 (d, *J* = 8.1 Hz, 1H), 5.90 (s, 1H), 4.78 (d, *J* = 12.5 Hz, 1H), 4.24 (d, *J* = 12.5 Hz, 1H), 1.26 (s, 9H). ^{13}C NMR (100 MHz, δ, $CDCl_3$, 298 K): 173.2, 167.6, 155.7, 143.7, 137.4, 129.9, 129.8, 129.5, 128.7, 128.6, 127.5, 126.1, 124.4, 84.8, 81.2, 55.7, 55.3, 27.8. HRMS (ESI): calcd *m/z* for $C_{22}H_{20}BrNO_6$: 496.0372 $[M+Na]^+$; found: 496.0366. HPLC (YMC Chiral ART Amylose-SA, eluent: hexane:*i*-PrOH = 90:10, 1 mL/min, 10 °C), retention times: $t_{minor\ d1}$=14.5 min, $t_{major\ d1}$= 27.5 min, $t_{minor\ d2}$=18.5 min, $t_{major\ d2}$= 35.4 min.

Reductive Cleavage of the Isoxazolidin-5-one N-O Bond.



7a **8**

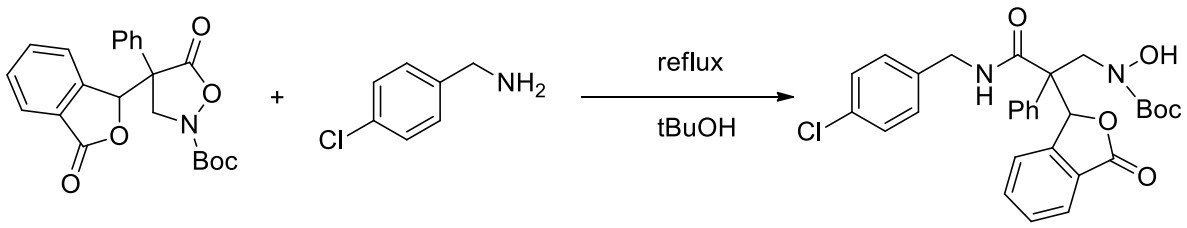
Under an Argon atmosphere, product **7a** (0.06 mmol), HCO_2NH_4 (0.6 mmol) and Pd/C (10% w/w) were placed in a round bottom flask and tBuOH (2 mL) was added. The suspension was stirred vigorously at r.t. for 20 h. After completion of the reaction, the mixture was filtered through a short pad of Celite® (washed with DCM). The solvent was removed in vacuo and then purified by flash chromatography (Chloroform:Methanol= 9:1) to obtain product **8** in 54% isolated yield (13 mg, 0.032 mmol).



8

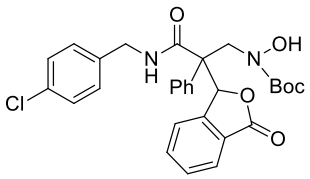
^{1}H NMR (300 MHz, δ, $CDCl_3$, 298 K): 7.80 (d, *J* = 8.2 Hz, 1H), 7.60 (t, *J* = 7.6 Hz, 2H), 7.42 (t, *J*= 7.6 Hz, 1H), 7.15 (t, *J*= 7.6 Hz, 5H), 6.52 (s, 1H), 5.88-5.73 (m, 2H), 4.68 (d, *J*= 15.3 Hz, 1H), 4.40 (d, *J*= 15.3 Hz, 1H), 1.41 (s, 9H). ^{13}C NMR (125 MHz, δ, $CDCl_3$, 298 K): 173.1, 169.2, 155.8, 144.9, 134.3, 133.9, 130.2, 130.1, 129.7, 129.5, 129.4, 129.4, 129.4, 129.1, 128.3, 128.2, 127.5, 127.5, 127.5, 126.6, 125.9, 125.5, 125.4, 124.4, 84.7, 81.2, 55.7, 54.3, 28.3, 27.8. HRMS (ESI): calcd *m/z* for $C_{22}H_{22}NO_6$: 396.1447 $[M-H]^+$; found: 396.1450.

Nucleophilic Ring-Opening of the Isoxazolidin-5-one.



7a **9**

In a pressure Schlenk-tube, product **7a** (0.06 mmol) and p-chloro benzylamine (0.06 mmol) were dissolved in tBuOH and stirred at 90 °C overnight. Volatiles were removed in vacuo and the crude mixture was purified by column chromatography (silica gel, heptanes/EtOAc) to yield amide **9** (16 mg, 0.029 mmol).

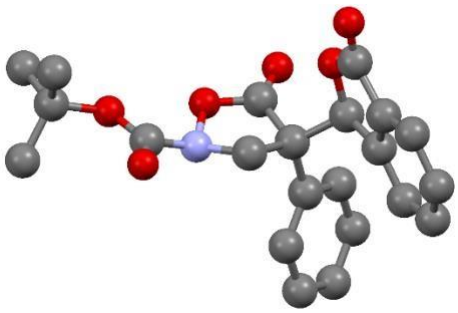


9

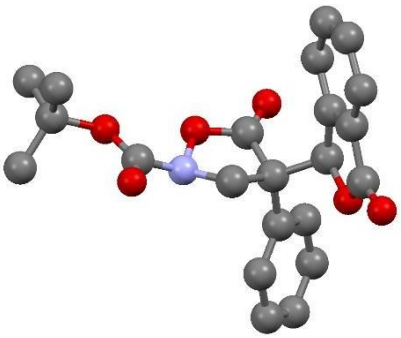
^{1}H NMR (300 MHz, δ, $CDCl_3$, 298 K): 7.81-7.77 (m, 1H), 7.62-7.55 (m, 2H), 7.45-7.40 (m, 1H), 7.32-7.29 (m, 1H), 7.24-7.16 (m, 5H), 7.07 (d, *J* = 8.2 Hz, 3H), 6.55 (s, 1H), 6.05 (t, *J*= 5.7 Hz, 1H), 4.62 (d, *J*= 14.8 Hz, 1H), 4.42 (d, *J*= 14.8 Hz, 2H), 4.14 (dd, J_1= 5.1 Hz, J_2 = 9.1 Hz, 1H), 1.37 (s, 9H). ^{13}C NMR (75 MHz, δ, $CDCl_3$, 298 K): 169.8, 156.7, 146.8, 135.9, 133.8, 133.4, 129.9, 129.5, 129.3, 128.9, 128.9, 128.8, 128.7, 128.1, 126.7, 125.3, 82.8, 59.6, 55.2, 43.4, 28.1. HRMS (ESI): calcd *m/z* for $C_{29}H_{29}ClN_2O_6$: 559.1612 $[M+Na]^+$; found: 559.1603.

Computational Details

To assess the relative configuration, DFT calculations were performed using Gaussian 16. To this end, the structure of compound **7a** was optimized in both *R,R*- and *R,S*-configuration using (keeping the stereocenter of the isoxazolidine configured as *R*) using B3LYP/6-31G(d). Applying this method, possible conformations were investigated and the structures lowest in energy were reoptimized using B3LYP/6-311+G(2d,p). For all optimizations performed, the implicit solvent description IEFPCM for chloroform as polarized continuum wasused as implemented in Gaussian 16.



R,S-**7a**



R,R-**7a**

ΔE = +0.6 kJ mol^{-1}

Figure S1. The two optimized structures for the two diastereomers of **7a**, hydrogen atoms omitted for clarity.

For each diastereomeric structure lowest in energy, isotropic chemical shifts for ^{13}C were computed by GIAO-NMR calculateions, applying different methods and scaling parameters as reported by Pierens[3] (Table S1). The methods were chosen according to their performance for ^{13}C-NMR predictions in chloroform and their accuracy for a compound of similar complexity and size (Mexicalin).

Table S1. Methods and scaling parameters used for the ^{13}C-NMR calculations to deliver the corresponding shifts relative to TMS as reference. In all cases, the IEFPCM description for chloroform

as solvent was added.

Abbreviation	Method/Basis set	Slope	Intercept
M1	B3LYP/6-311+G(2d,p)	-1.0427	181.7173
M2	mPW1PW91/6-311+G(2d,p)	-1.0420	186.3567
M3	PBE0/6-311+G(2d,p)	-1.0423	187.1937
M4	B3LYP/aug-cc-pvdz	-0.9974	190.9642

Calculated shifts (relative to tetramethylsilane (TMS)) are given in Table S2 and Table S3, respectively. The atom numbering in the Tables correspond to the atom numbers in the coordinate lists. The assigned numbers do not change between the two diastereomers and are shown for *R,R*-**7a** in Figure S2.

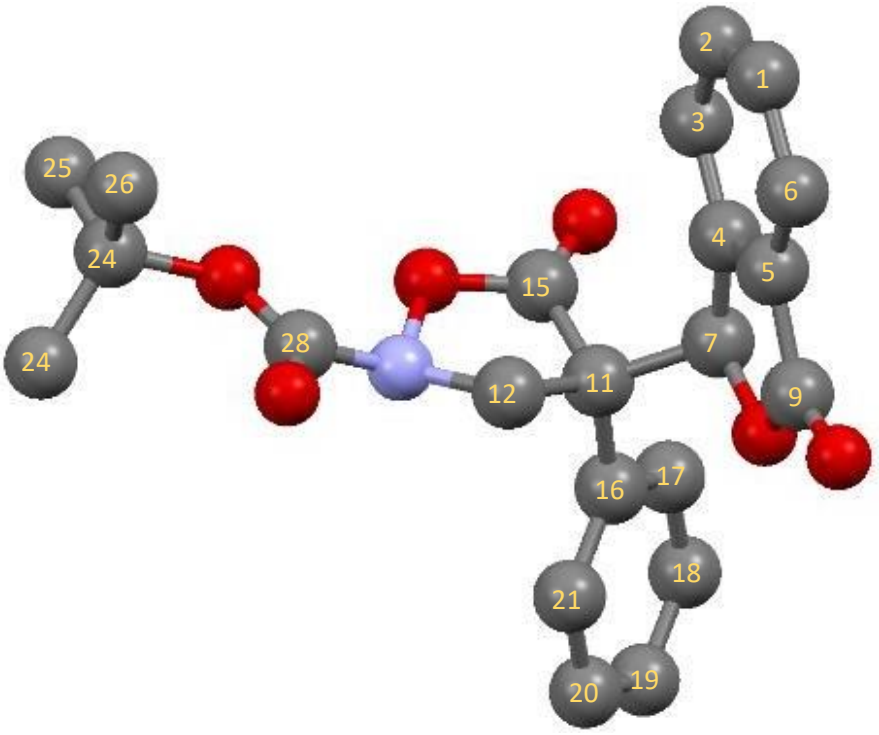


Figure S2. Carbon atom numbering demonstrated for the *R,R*-structure. The other diastereomer's atom assignment is identical.

For equivalent carbons 17&20 (*ortho*-C of the phenyl group), 18&21 (*meta*-C of the phenyl group) and 25-27(methyl groups in *t*-Bu group), due to the non-dynamic nature of the calculations, different shifts with high anisotropy were obtained from the calculations. Unweighted averages were calculated for these atoms and arerepresented as such in the Tables S2-S6. Further analyses ($MAE_{\Delta\delta}$, $MAE_{\Delta\Delta\delta}$), were carried out accounting forall atoms (indicated by the index: *all*) and, as well as without taking those averaged signals into account (indicated by the index: *sel*).

Table S2. Experimentally obtained ^{13}C-NMR shifts compared to the computationally obtained shifts for the *unlike*-configuration (*R,S*). Experimental shifts were referenced to the solvent signal, calculated values are relative to TMS.

Atom-	Experimental shifts: δ_{exp} / ppm		Computational shifts: δ_{RS} / ppm			
Nr.	major	minor	M1	M2	M3	M4
C-1	130.1	130.3	132.0	132.1	132.1	127.4
C-2	134.3	134.4	136.5	136.7	136.7	131.2
C-3	124.4	123.5	124.5	124.7	124.7	120.5
C-4	144.9	144.7	150.4	149.4	149.4	145.5
C-5	126.6	126.8	128.7	128.3	128.2	126.0
C-6	125.9	126.2	127.6	128.1	128.1	122.6
C-7	81.2	81.3	81.0	79.7	79.7	83.7
C-9	169.2	169.0	175.5	174.6	174.5	170.1
C-11	55.7	57.5	56.0	55.0	54.9	60.9
C-12	54.3	56.7	44.0	43.2	43.2	47.7
C-15	173.1	172.0	178.0	176.8	176.7	172.3
C-16	129.7	129.8	135.0	133.7	133.7	133.0
C-17/21	127.5	127.8	129.2	129.2	129.2	125.1
C-18/20	129.4	129.7	131.3	131.4	131.5	126.3
C-19	130.2	133.3	131.5	131.7	131.7	126.3
C-24	84.7	84.5	87.2	85.6	85.5	89.6
C-25-27	27.8	27.8	19.7	19.6	19.7	25.7
C-28	155.8	156.0	161.0	160.2	160.1	156.6
C-17			130.6	130.6	130.6	126.5
C-18			131.6	131.7	131.8	126.7
C-20			130.9	131.1	131.1	125.9
C-21			127.7	127.8	127.7	123.7
C-25			23.4	23.1	23.2	29.7
C-26			18.1	18.1	18.2	24.2
C-27			17.5	17.6	17.7	23.4

Table S3. Experimentally obtained ^{13}C-NMR shifts compared to the computationally obtained shifts for the *like*-configuration (*R*,*R*). Experimental shifts were referenced to the solvent signal, calculated

values are relative to TMS.

Atom-Nr.	Experimental shifts: δ_{exp} / ppm major	minor	Computational shifts: δ_{RS} /ppm M1	M2	M3	M4
C-1	130.1	130.3	132.2	132.3	132.4	127.3
C-2	134.3	134.4	137.4	137.5	137.6	131.7
C-3	124.4	123.5	124.9	125.1	125.0	121.3
C-4	144.9	144.7	150.5	149.3	149.3	145.4
C-5	126.6	126.8	129.1	128.6	128.6	125.9
C-6	125.9	126.2	128.0	128.4	128.4	123.4
C-7	81.2	81.3	85.5	84.0	84.1	87.4
C-9	169.2	169.0	175.0	174.2	174.1	169.5
C-11	55.7	57.5	57.6	56.5	56.4	62.1
C-12	54.3	56.7	45.8	45.0	45.0	49.4
C-15	173.1	172.0	178.6	177.5	177.4	172.8
C-16	129.7	129.8	137.1	135.8	135.8	134.7
C-17/21	127.5	127.8	128.3	128.4	128.3	124.2
C-18/20	129.4	129.7	130.9	131.0	131.1	125.9
C-19	130.2	133.3	130.9	131.1	131.1	126.2
C-24	84.7	84.5	87.4	85.7	85.6	89.8
C-25-27	27.8	27.8	19.6	19.5	19.6	25.7
C-28	155.8	156.0	160.6	159.8	159.7	156.4
C-17			129.4	129.4	129.4	125.0
C-18			131.1	131.2	131.3	126.0
C-20			130.6	130.7	130.8	125.8
C-21			127.2	127.3	127.2	123.4
C-25			23.3	23.0	23.1	29.8
C-26			18.1	18.1	18.2	24.1
C-27			17.4	17.5	17.5	23.3

$MAE_{\Delta\delta}$ analysis

A mean absolute error (MAE) analysis was performed. For each method, the absolute differences in chemicalshift $\Delta\delta = | \delta_{exp} - \delta_{calc} |$ were calculated between the experimental shifts for major and minor diastereomer andthe calculated shifts for the *R*,*S*-structure (Table S4) and the *R*,*R*-configuration (Table S5), respectively. The obtained $MAE_{\Delta\delta}$ values were found to be generally quite large, even when omitting the averaged shift mentioned above. Additionally, in the results for all methods, both for the *like*- and *unlike*-isomer, lower MAEvalues for the major product were obtained. Hence, this method was disregarded.

Table S4. Absolute deviations in chemical shift $\Delta\delta = | \delta_{exp} - \delta_{calc} |$ for the *unlike*-configuration (*R*,*S*). Mean absolute errors calculated for all carbons ($MAE_{\Delta\delta,all}$) and for a selection ($MAE_{\Delta\delta,sel}$) excluding highly anisotropic shifts due to the static nature of the calculations (*t*-Bu-group, carbons in *o*- and *m*-position of Ph).

Atom-	**M1:Δδ**		**M2: Δδ**		**M3: Δδ**		**M4: Δδ**	
Nr.	**maj-RS**	**min-RS**	**maj-RS**	**min-RS**	**maj-RS**	**min-RS**	**maj-R**	**min-RS**
C-1	1.88	1.67	1.98	1.77	1.99	1.78	2.70	2.91
C-2	2.28	2.19	2.46	2.36	2.44	2.35	3.01	3.11
C-3	0.18	1.08	0.36	1.26	0.34	1.24	3.83	2.93
C-4	5.54	5.75	4.49	4.70	4.50	4.71	0.57	0.78
C-5	2.17	1.90	1.70	1.43	1.69	1.42	0.60	0.87
C-6	1.74	1.45	2.22	1.93	2.20	1.91	3.24	3.53
C-7	0.23	0.30	1.50	1.57	1.47	1.54	2.53	2.46
C-9	6.24	6.42	5.38	5.56	5.30	5.48	0.84	1.02
C-11	0.25	1.46	0.79	2.50	0.86	2.57	5.15	3.44
C-12	10.26	12.62	11.09	13.45	11.14	13.50	6.59	8.95
C-15	4.82	5.95	3.66	4.79	3.58	4.71	0.84	0.29
C-16	5.23	5.13	3.94	3.84	3.98	3.88	3.25	3.15
C-17/21	1.66	1.34	1.68	1.36	1.65	1.33	2.40	2.72
C-18/20	1.91	1.59	2.05	1.73	2.11	1.79	3.07	3.39

C-19	1.29	1.81	1.48	1.61	1.52	1.57	3.85	6.94
C-24	2.58	2.70	0.91	1.03	0.84	0.96	4.95	5.07
C-25-27	8.14	8.09	8.20	8.15	8.12	8.07	2.06	2.01
C-28	5.13	5.00	4.38	4.25	4.26	4.13	0.79	0.66
MAE$\Delta\delta$,all	**3.42**	**3.69**	**3.24**	**3.52**	**3.22**	**3.50**	**2.79**	**3.01**
MAE$\Delta\delta$,sel	**3.61**	**3.84**	**3.41**	**3.65**	**3.39**	**3.63**	**2.73**	**3.02**

Table S5. Absolute deviations in chemical shift $\Delta\delta = | \delta_{exp} - \delta_{calc} |$ for the *like*-configuration (*R*,*R*). Mean absolute errors calculated for all carbons ($MAE_{\Delta\delta,all}$) and for a selection ($MAE_{\Delta\delta,sel}$) excluding highly anisotropic shifts due to the static nature of the calculations (*t*-Bu-group, carbons in *o*- and *m*-position of Ph).

Atom-	**M1: $\Delta\delta$**		**M2: $\Delta\delta$**		**M3: $\Delta\delta$**		**M4: $\Delta\delta$**	
Nr.	**maj-RR**	**min-RR**	**maj-RR**	**min-RR**	**maj-RR**	**min-RR**	**maj-RR**	**min-RR**
C-1	2.13	1.92	2.25	2.04	2.30	2.09	2.79	3.00
C-2	3.16	3.06	3.28	3.18	3.30	3.20	2.51	2.60
C-3	0.50	1.40	0.70	1.60	0.69	1.59	3.02	2.12
C-4	5.55	5.76	4.39	4.60	4.41	4.62	0.46	0.67
C-5	2.54	2.27	2.09	1.82	2.07	1.80	0.67	0.94
C-6	2.09	1.80	2.56	2.27	2.51	2.22	2.45	2.74
C-7	4.29	4.22	2.85	2.78	2.88	2.81	6.24	6.17
C-9	5.80	5.98	4.96	5.14	4.89	5.07	0.29	0.47
C-11	1.90	0.19	0.74	0.97	0.68	1.03	6.35	4.64
C-12	8.51	10.87	9.28	11.64	9.34	11.70	4.92	7.28
C-15	5.43	6.56	4.31	5.44	4.22	5.35	0.31	0.82
C-16	7.35	7.25	6.05	5.95	6.09	5.99	4.93	4.83
C-17/21	0.77	0.45	0.83	0.51	0.79	0.47	3.35	3.67
C-18/20	1.48	1.16	1.62	1.30	1.69	1.37	3.45	3.77
C-19	0.69	2.41	0.88	2.21	0.93	2.17	3.98	7.08

C-24	2.70	2.82	1.03	1.15	0.97	1.09	5.15	5.27
C-25-27	8.23	8.18	8.29	8.24	8.21	8.16	2.09	2.04
C-28	4.71	4.58	3.95	3.82	3.83	3.70	0.54	0.41
MAE$\Delta\delta$,all	**3.77**	**3.94**	**3.34**	**3.59**	**3.32**	**3.58**	**2.97**	**3.25**
MAE$\Delta\delta$,sel	**3.96**	**4.09**	**3.49**	**3.71**	**3.48**	**3.70**	**2.97**	**3.32**

MAE$\Delta\Delta\delta$ analysis

Since simple MAE (mean absolute error) analyses remained inconclusive and generally showed quite high deviations, an MAE$\Delta\Delta\delta$ approach as reported by the group of Bifulco was undertaken.

Herein, the term $\Delta\Delta\delta = |\ \Delta\delta_{calc} - \Delta\delta_{exp}\ |$ is calculated as the absolute difference in chemical shift $\Delta\delta_{calc}$ between the calculated diastereomers (*R*,*S* and *R*,*R*) and the difference in chemical shift $\Delta\delta_{exp}$ obtained experimentally.Two separate values for $\Delta\Delta\delta$ are then calculated for each atom with both $\Delta\delta_{exp} = \delta_{major} - \delta_{minor}$ as well as

$\Delta\delta_{exp} = \delta_{minor} - \delta_{major}$. In this context, the calculation with the difference $\Delta\delta_{exp} = \delta_{major} - \delta_{minor}$ corresponds to thecorrelation between the *R*,*S*-isomer and the major product (*vice versa*), which is ultimately accounted for all atoms as the $MAE_{\Delta\Delta\delta}$.

As can be seen from the results in Table S6, with all methods, a clearly better correlation between the *unlike*- isomer and the experimentally observed major diastereomer was obtained as compared to the minor one. Theselected atom set (discarded *o*- and *m*-carbons of the Ph group as well as Me-signals from the *t*-Bu group), yielded even higher differences in the $MAE_{\Delta\Delta\delta}$. This leads us to assume an *unlike*-configuration for the majordiastereoisomer.

Table S6. Results of the $MAE_{\Delta\Delta\delta}$ assessment. Mean absolute errors calculated for all carbons ($MAE_{\Delta\Delta\delta,all}$) andfor a selection ($MAE_{\Delta\Delta\delta,sel}$) excluding highly anisotropic shifts due to the static nature of the calculations (*t*- Bu-group, aromatic carbons in ortho- and meta-position).

Atom-Nr.	M1: ΔΔδ		M2: ΔΔδ		M3:ΔΔδ		M4:ΔΔδ	
	RS-RR.	**RS-RR**	**RS-RR.**	**RS-RR**	**RS-RR.**	**RS-RR**	**RS-RR.**	**RS-RR**
	maj-min	**min-maj**	**maj-min**	**min-maj**	**maj-min**	**min-maj**	**maj-min**	**min-maj**
C-1	0.04	0.46	0.06	0.48	0.10	0.52	0.30	0.12
C-2	0.88	0.88	0.82	0.82	0.86	0.86	0.50	0.50
C-3	1.21	0.59	1.23	0.57	1.25	0.55	1.71	0.09
C-4	0.23	0.20	0.11	0.31	0.12	0.31	0.10	0.32
C-5	0.09	0.63	0.12	0.66	0.11	0.65	0.34	0.20
C-6	0.06	0.64	0.05	0.63	0.03	0.61	0.50	1.08
C-7	4.44	4.58	4.27	4.41	4.28	4.42	3.64	3.78
C-9	0.26	0.62	0.24	0.60	0.24	0.60	0.37	0.73
C-11	0.06	3.36	0.18	3.24	0.17	3.25	0.52	2.90
C-12	0.61	4.11	0.54	4.18	0.56	4.16	0.69	4.03
C-15	1.73	0.53	1.79	0.47	1.77	0.49	1.66	0.60
C-16	2.03	2.23	2.01	2.21	2.00	2.20	1.58	1.78
C-17/21	1.21	0.57	1.17	0.53	1.17	0.53	1.27	0.63
C-18/20	0.75	0.11	0.76	0.12	0.74	0.10	0.70	0.06
C-19	3.69	2.50	3.70	2.50	3.69	2.50	3.23	2.96
C-24	0.24	0.00	0.25	0.01	0.25	0.01	0.31	0.07
C-25-27	0.04	0.14	0.04	0.14	0.04	0.14	0.02	0.08
C-28	0.55	0.29	0.56	0.30	0.56	0.30	0.38	0.12
MAEΔΔδ,all	**1.06**	**1.25**	**0.99**	**1.23**	**1.00**	**1.23**	**0.99**	**1.11**
MAEΔΔδ,sel	**1.17**	**1.46**	**1.16**	**1.44**	**1.16**	**1.44**	**1.16**	**1.34**

Coordinates of the optimized geometries 7a

***R,S*-7a**

E (IEFPCM($CHCl_3$)-B3LYP/6-311+G(2d,p)) = -1357.492694

C	4.45403	-2.33810	-1.73917	C	-5.11023	-1.94299	-0.47075
C	4.47118	-0.93932	-1.74754	C	-5.47581	0.27886	-1.65365
C	3.66595	-0.19568	-0.88728	C	-2.65627	-0.19718	-0.69913
C	2.83228	-0.88721	-0.01744	O	-2.59204	-0.76895	-1.76761
C	2.82752	-2.27563	-0.00726	H	5.09418	-2.88444	-2.42033
C	3.62881	-3.02617	-0.85979	H	5.12802	-0.42185	-2.43613
C	1.87296	-0.40561	1.04355	H	3.70004	0.88503	-0.90368
O	1.33921	-1.62488	1.61513	H	3.60687	-4.10814	-0.82996
C	1.88727	-2.73741	1.02622	H	2.39245	0.11167	1.85064
O	1.58494	-3.84973	1.36962	H	0.06299	-0.03171	-1.49702
C	0.70615	0.49091	0.56068	H	-0.22752	-1.28181	-0.28120
C	-0.19921	-0.20475	-0.45955	H	2.05602	2.29701	2.09150
N	-1.50635	0.40011	-0.17360	H	2.95832	4.48718	1.47767
O	-1.55788	0.64108	1.24966	H	2.63103	5.37975	-0.81680
C	-0.28511	0.70933	1.71695	H	1.37809	4.03181	-2.48132
C	1.22926	1.87878	0.14291	H	0.49051	1.84377	-1.88782
C	1.92094	2.65631	1.07950	H	-5.87671	1.13981	0.91796
C	2.42516	3.90464	0.73626	H	-6.98306	-0.21283	0.62846
C	2.23999	4.40590	-0.54843	H	-5.61941	-0.40829	1.74180
C	1.54023	3.64995	-1.48071	H	-4.50072	-2.29589	-1.30013
C	1.03666	2.39804	-1.13791	H	-6.14021	-2.26624	-0.63502
O	-0.05976	0.93164	2.87189	H	-4.75479	-2.40190	0.45378
O	-3.71732	0.02505	0.05673	H	-6.52085	0.05250	-1.87497
C	-5.08133	-0.42174	-0.35697	H	-5.37881	1.36116	-1.54818
C	-5.94103	0.05616	0.80847	H	-4.86571	-0.05352	-2.49120

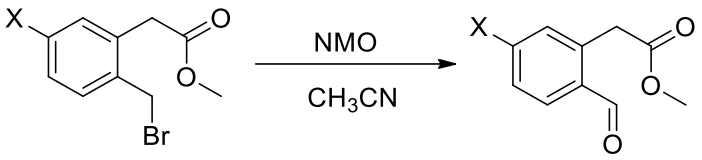
***R,R*-7a**

E (IEFPCM($CHCl_3$)-B3LYP/6-311+G(2d,p)) = -1357.491234

C	2.20865	-4.45548	0.36091	C	-4.87790	-1.85054	-0.61014
C	1.60480	-3.83890	1.46150	C	-5.43988	0.56402	-1.17884
C	1.54635	-2.45138	1.57848	C	-2.51579	0.03326	-0.69664
C	2.10103	-1.68952	0.55768	O	-2.56830	-0.27903	-1.86757
C	2.71038	-2.30805	-0.52557	H	2.23853	-5.53625	0.30350
C	2.77671	-3.69068	-0.64953	H	1.17734	-4.45325	2.24458
C	2.23940	-0.19468	0.38632	H	1.08844	-1.99378	2.44497
O	2.95298	-0.05023	-0.86600	H	3.26031	-4.14710	-1.50390
C	3.24636	-1.26994	-1.42061	H	2.86996	0.22715	1.17040
O	3.84526	-1.36525	-2.45969	H	0.06865	0.53833	-1.74634
C	0.94912	0.66024	0.28779	H	-0.00522	-0.95920	-0.81233
C	-0.04761	0.13143	-0.74938	H	2.15068	2.28063	2.11746
N	-1.32963	0.56964	-0.18469	H	2.82448	4.62651	1.91569
O	-1.20492	0.47500	1.25180	H	2.37194	5.88396	-0.17811
C	0.11336	0.52641	1.56619	H	1.23731	4.73982	-2.06488
C	1.31803	2.15211	0.13293	H	0.57427	2.40651	-1.88066
C	1.95494	2.80759	1.19212	H	-5.54159	0.77739	1.55188
C	2.33292	4.14005	1.08192	H	-6.64206	-0.52675	1.07745
C	2.07852	4.84496	-0.09009	H	-5.14704	-0.90447	1.94862
C	1.44255	4.20418	-1.14599	H	-4.36588	-1.96668	-1.56312
C	1.06390	2.86911	-1.03565	H	-5.91191	-2.18037	-0.72981
O	0.47813	0.47019	2.70808	H	-4.40162	-2.49403	0.13216
O	-3.47822	0.01073	0.20926	H	-6.49844	0.34134	-1.32763
C	-4.87224	-0.39881	-0.14050	H	-5.35663	1.59505	-0.82984
C	-5.59258	-0.25257	1.19563	H	-4.92962	0.46955	-2.13530

5.6 3-Isoquinolones: genral procedures and spectroscopic data

General procedure for synthesis of Aldehyde A.

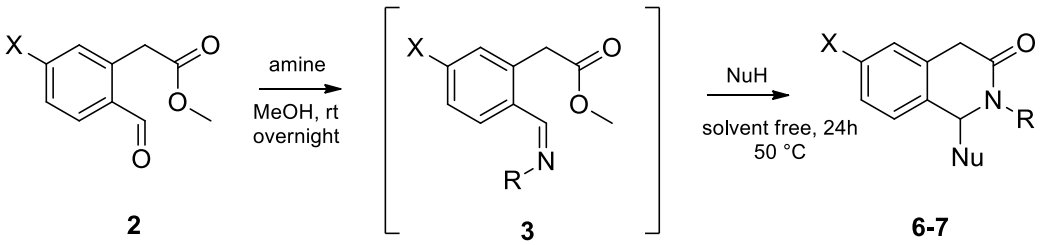


1a X= H
1b X= OCH_3

2a X= H
2b X= OCH_3

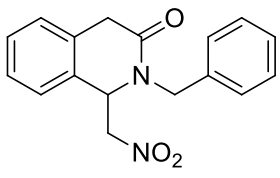
In a round bottom flask containing the bromide derivative **1** (13.2 mmol), was added CH_3CN (25 mL) followed by N-Methylmorpholine N-oxide (39.6 mmol) and the reaction mixture was stirred for 2h. Then the reaction was quenched with a solution of H_2O (82 mL) and $Na_2S_2O_3$ (21 g) and extracted with Ethyl acetate. The resulting organic layer was washed with $NaHCO_3$ sat. solution and dried with Na_2SO_2. The solvent was removed under reduced pressure and the crude product purified by chromatography on silica (Hexane/Ethyl acetate, 5:1) affording the pure Aldehyde **2**. (Yield=>99%)

General procedure for Mannich/lactamization reaction. (3-4)



2 **3** **6-7**

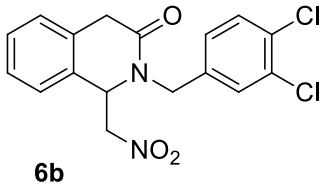
Methyl 2-(2-formylphenyl)acetate (**A**) (0.15 mmol, 1.0 eq.) was treated with the amine (0.15 mmol, 1.0 eq.) at rt in MeOH (0.3 mL) for 18h. After solvent evaporation, the crude product imine (**2**) was reacted with the pronucleophile NuH (1.5 mmol, 10 eq.) at 50°C (oil bath) for 24h. Then the product was directly purified by chromatography on silica gel (Hexane/Ethyl acetate, 7:3) affording the corresponding products (**3-4**).



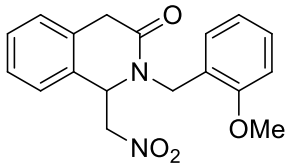
6a

2-benzyl-1-(nitromethyl)-1,2-dihydroisoquinolin-3(4H)-one.(**6a**). Compound was obtained as a yellow oil in 99% yield (44 mg).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.21 (m, 8H), 7.04 (d, *J= 7.5 Hz*, 1H), 5.27 (d, *J=15.1 Hz*, 1H), 5.10 (t, *J*= 6.7Hz, 1H), 4.50-4.43 (m, 2H), 4.32 (d,

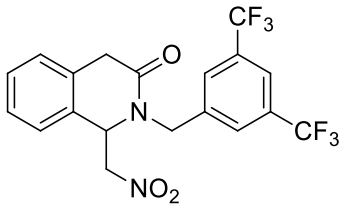
J=15.1 Hz, 1H), 3.75 (s, 2H).^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 136.1, 132.2, 130.9, 129.3, 129.2, 128.3, 128.2, 127.6, 125.9, 77.7, 58.9, 49.1, 37.4. IR (neat): 2923, 1652, 1553, 1451, 1379, 1260, 758, 732 cm-^{1}. HRMS (MALDI-FT ICR): *m/z* calcd. for $[C_{17}H_{16}N_2O_3 + H]^+$: 297.1233; found: 297.1226.



6b ***2-(3,4-dichlorobenzyl)-1-(nitromethyl)-1,2-dihydroisoquinolin-3(4H)-one.*****(6b).** Compound was obtained as a yellow solid in 73% yield (40 mg) Mp 121−123 °C.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.23 (m, 5H), 7.09-7.01 (m, 3H), 5.31 (d, *J*= 15.8 Hz, 1H), 5.09 (t, *J*= 6.5 Hz, 1H), 4.61-4.47 (m, 2H), 4.11 (d, *J*= 15.8 Hz, 1H), 3.75 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 136.5, 133.2, 132.3, 132.0, 131.1, 130.5, 130.1, 129.6, 128.4, 127.8, 127.3, 125.8, 77.9, 59.2, 48.1, 37.3. IR (KBr disc): 2918, 2360, 1663, 1471, 1421, 1380, 1264, 1029, 761 cm^{-1}. HRMS (MALDI-FT ICR): *m/z* calcd. for $[C_{17}H_{14}Cl_2N_2O_3 + H]^+$: 365.0454; found: 365.0478.

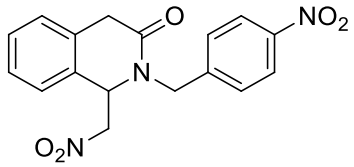


6c ***2-(2-methoxybenzyl)-1-(nitromethyl)-1,2-dihydroisoquinolin-3(4H)-one.*****(6c)** Compound was obtained as a red solid in 70% yield (34 mg). Mp 115−1117 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.23 (m, 1H), 7.21-7.19 (m, 3H), 7.07 (d, *J*= 7.6 Hz, 1H), 6.89-6.86 (m, 3H), 5.26 (dd, J_1= 5.2 Hz, J_2= *2*.9 Hz, 1H), 5.10 (d, *J*= 14.8 Hz, 1H), 4.59 (dd, J_1= 7.1 Hz, J_2= 5.2 Hz, 1H), 4.52-4.44 (m, 2H), 3.84 (s, 3H), 3.70 (s, 2H).^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 157.7, 132.3, 131.3, 130.6, 129.5, 129.2, 128.2, 127.4, 126.0, 124.2, 121.1, 110.6, 59.3, 55.5, 44.1, 37.4. IR (KBr disc): 2923, 2360, 1661, 1642, 1549, 1455, 1252, 1025, 759 cm^{-1}. HRMS (MALDI-FT ICR): *m/z* calcd. for $[C_{18}H_{18}N_2O_4 + H]^+$: 327.1339; found: 327.1318.



6d ***2-(3,5-bis(trifluoromethyl)benzyl)-1-(nitromethyl)-1,2-dihydroisoquinolin-3(4H)-one.*****(6d)** Compound was obtained as a yellow oil in 73% yield (46 mg).^{1}H NMR(300 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.60 (s, 2H), 7.38 (t, *J*= 7.7 Hz, 1H), 7.28 (t, *J*= 6.3 Hz, 2H), 7.11 (d, *J*= 7.7 Hz, 1H), 5.47 (d, *J*= 15.3 Hz, 1H), 5.12 (t, *J*= 6.8 Hz, 1H), 4.68-4.50 (m, 2H), 4.28 (d, *J*= 15.3 Hz, 1H), 3.79 (s, 2H).^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7, 139.0, 132.3 (q, J_{CF}= *34.4 Hz)*

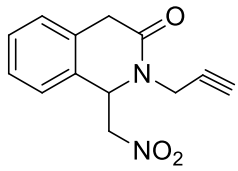
131.9, 130.3, 129.7, 128.5, 127.9, 125.7, 124.9, 122.1, 121.3, 77.9, 59.8, 48.8, 37.3. IR (KBr disc): 2925, 2853, 1687, 1682, 1558, 1455, 1382, 1173, 1126, 758, 739 cm^{-1}. HRMS (MALDI-FT ICR): *m/z* calcd. for $[C_{19}H_{14}F_6N_2O_3 + H]^+$: 433.0981; found: 433.1017.



6e

***2-(4-nitrobenzyl)-1-(nitromethyl)-1,2-dihydroisoquinolin-3(4H)-one*.**

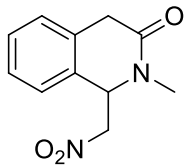
(6e) Compound was obtained as a orange solid in 98% yield (50 mg). Mp 134−136 °C.^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J*= 8.8 Hz, 2H), 7.39-7.25 (m, 5H), 7.09 (d, *J*= 7.6 Hz, 1H), 5.47 (d, *J*=15.8 Hz, 1H), 5.10 (t, *J*= 6.7 Hz, 1H), 4.66-4.50 /m, 2H), 4.24 (d, *J*=15.8 Hz, 1H), 3.78 (s, 2H).^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 147.8, 143.7, 132.0, 130.4, 129.7, 128.6. 128.5, 127.9, 125.8, 124.3, 78.0, 59.6, 48.7, 37.3. IR (KBr disc): 2361, 1654, 1601, 1552, 1516, 1453, 1344, 732 cm^{-1}. HRMS (MALDI-FT ICR): *m/z* calcd. for $[C_{17}H_{15}N_3O_5 + H]^+$: 342.1084; found: 342.1097.



6f

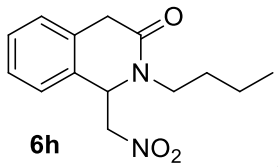
***1-(nitromethyl)-2-(prop-2-yn-1-yl)-1,2-dihydroisoquinolin-3(4H)-on.e*(6f).**

Compound was obtained as a orange oil in 78% yield (29 mg).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.20 (m, 4H), 5.46 (t, *J*= 6.7 Hz, 1H), 4.87 (dd, J_1= 6.7 Hz, J_2= 5.9 Hz, 1H), 4.63-4.55 (m, 2H), 4.28 (dd, J_1= 15.6 Hz, J_2= 2.2 Hz, 1H), 3.69 (s, 2H), 2.35 (t, *J*=2.2 Hz, 1H).^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 131.9, 130.6, 129.4, 128.3, 127.6, 126.1, 77.7, 74.0, 59.1, 37.1, 35.3. IR (KBr disc): 1652, 1553, 1451, 1265cm^{-1}. HRMS (MALDI-FT ICR): *m/z* calcd. for $[C_{13}H_{12}N_2O_3 + H]^+$: 245.0920; found: 245.0913.



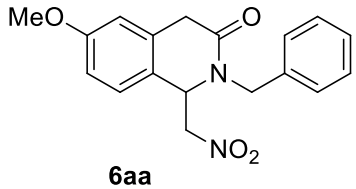
6g

***2-methyl-1-(nitromethyl)-1,2-dihydroisoquinolin-3(4H)-one*.(6g)** Compound was obtained as a yellow oil in 80% yield (26 mg).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.18 (m, 4H), 5.14 (t, *J*= 6.4 Hz, 1H), 4.69-4,50 (m, 2H), 3.65 (s, 2H), 3.13 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 132.3, 130.3, 129.3, 128.3, 127.5, 125.9, 78.0, 62.3, 36.8, 34.4. IR (KBr disc): 2361, 2342, 1654, 1555, 1449, 1400, 1379, 758 cm^{-1}. HRMS (MALDI-FT ICR): *m/z* calcd. for $[C_{11}H_{12}N_2O_3 + H]^+$: 221.0920; found: 221.0924.



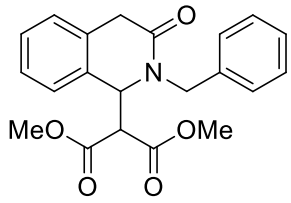
6h

***2-butyl-1-(nitromethyl)-1,2-dihydroisoquinolin-3(4H)-one.*(6h)** Compound was obtained as a orange oil in 60% yield (23 mg).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.18 (m, 4H), 5.14 (t, *J*= 6.3 Hz, 1H), 4.66-4.61 (m, 1H), 4.51-4.46 (m, 1H), 4.11-4.03 (m, 1H), 3.65 (s, 2H), 2.97-2.90 (m, 1H), 1.60-1.51 (m, 2H), 1.30-1.25 (m, 2H), 0.92-0.88 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 132.5, 131.0, 129.3, 128.3, 127.5, 125.9, 78.0, 59.9, 46.4, 37.4, 30.0, 20.2, 13.9. IR (KBr disc): 2958, 2928, 2360, 1652, 1635, 1562 cm^{-1}. HRMS (MALDI-FT ICR): *m/z* calcd. for $[C_{14}H_{18}N_2O_3 + H]^+$: 263.1390; found: 263.1382.



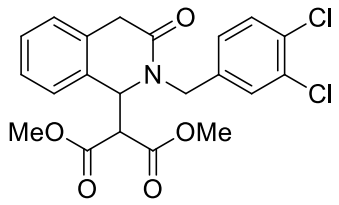
6aa

2-benzyl-6-methoxy-1-(nitromethyl)-1,2-dihydroisoquinolin-3(4H)-one (6aa). Prepared from compound **2b** (X= OCH_3) following the same procedure reported above. Compound was obtained as a orange oil in 83% yield (41 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.21 (m, 5H), 6.96 (d, *J*= 9.1 *Hz*, 1H), 6.75-6.74 (m, 2H), 5.28 (d, *J*= 14.7 *Hz*, 1H), 4.48-4.38 (m, 2H), 4.56 (d, *J*= 14.7 *Hz*, 1H), 3.81 (s, 3H), 3.73 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 160.2, 136.1, 133.7, 129.1, 128.0, 127.1, 122.8, 113.2, 78.6, 58.4, 55.5, 49.0, 37.6. IR (neat): 2920, 2362, 1666, 1640, 1458, 1252, 758 cm^{-1}. HRMS (MALDI-FT ICR): *m/z* calcd. for $[C_{18}H_{18}N_2O_4 + H]^+$: 327.1339; found: : 327.1352.

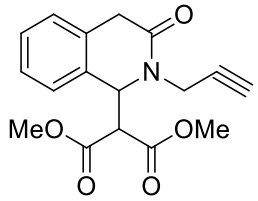


7a

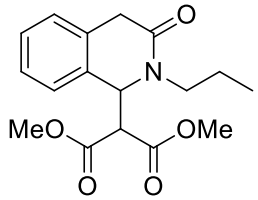
***Dimethyl 2-(2-benzyl-3-oxo-1,2,3,4-tetrahydroisoquinolin-1-yl)malonate.*(4a)** Compound was obtained as a yellow oil in 65% yield (36 mg).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23-7.02 (m, 9H), 5.44 (d, *J*= 14.7 Hz, 1H), 5.19 (d, *J*= 8.8 Hz, 1H), 4.07 (d, *J*= 14.7 Hz, 1H), 3.81-3.73 (m, 6H), 3.50 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.7, 168.9, 168.2, 137.7, 134.9, 134.1, 130.1, 130.0, 129.9, 129.1, 129.0, 128.8, 128.1, 127.3, 61.1, 58.2, 54.6, 54.1, 50.7, 39.5. IR (KBr disc): 2954, 2924, 2361, 1739, 1652, 1452, 1437 cm^{-1}. HRMS (MALDI-FT ICR): *m/z* calcd. for $[C_{21}H_{21}NO_5 + H]^+$: 368.1492; found: 368.1468.



7b ***dimethyl 2-(2-(3,4-dichlorobenzyl)-3-oxo-1,2,3,4-tetrahydroisoquinolin-1-yl)malonate.*****(7b)** Compound was obtained as a yellow solid in 55% yield (36 mg). Mp 119−121 °C.^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29-7.14 (m, 6H), 7.06 (d, *J= 7.3 Hz*, 1H), 6.93-6.91 (m, 1H), 5.33 (d, *J= 15.4 Hz*, 1H), 5.14 (d, *J*= 8.1 Hz, 1H), 4.07 (d, *J*= 15.4 Hz, 1H), 3.80-3.71 (m, 6H), 3.51 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 167.6, 166.8, 137.0, 133.3, 132.8, 132.5, 131.6, 130.7, 129.9, 128.8, 128.0, 127.1, 127.1, 126.0, 60.1, 57.0, 53.4, 52.9, 38.1. IR (KBr disc): 1748, 1661, 1473, 1433, 1399, 1147 cm^{-1}. HRMS (MALDI-FT ICR): *m/z* calcd. for $[C_{21}H_{19}Cl_2NO_5 + H]^+$: 436.0713; found: 436.0725.



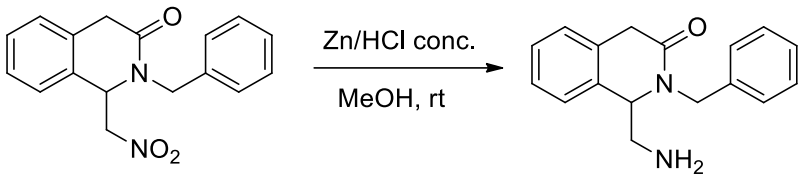
7c ***dimethyl 2-(3-oxo-2-(prop-2-yn-1-yl)-1,2,3,4-tetrahydroisoquinolin-1-yl)malonate.*****(7c)** Compound was obtained as a yellow oil in 74% yield (35 mg).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28-7.16 (m, 4H), 5.51 (d, *J*= 7.9 Hz, 1H), 4.76 (dd, J_1= 14.9 Hz, J_2= 2.4 Hz, 1H), 3.97 (dd, J_1= 14.9 Hz, J_2= 2.4 Hz, 1H), 3.84-3.65 (m, 6H), 3.52 (s, 3H), 2.20 (t, *J*= 2.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 167.5, 166.9, 133.1, 132.6, 128.7, 127.9, 126.9, 126.2, 78.3, 72.6, 60.1, 57.1, 53.4, 52.9, 37.9, 36.2. IR (KBr disc): 2361, 2237, 1734, 1662, 1449, 1437, 1157 cm^{-1}. HRMS (MALDI-FT ICR)**:** *m/z* calcd. for $[C_{17}H_{17}NO_5 + H]^+$: 316.1179; found: 316.1181



7d ***dimethyl 2-(3-oxo-2-propyl-1,2,3,4-tetrahydroisoquinolin-1-yl)malonate.*****(7d)** Compound was obtained as a yellow oil in 73% yield (34 mg).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27-7.16 (m, 4H), 5.19 (d, *J*= 9.1 Hz, 1H), 4.08-3.99 (m, 1H), 3.78-3.62 (m, 6H), 3.54 (s, 3H), 2.87-2.77 (m, 1H), 1.56-144 (m, 2H), 0.77 (t, *J*= 7.2 Hz, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 167.5, 167.0, 133.9, 133.2, 128.6, 127.9, 126.8, 126.0, 61.0, 56.8, 53.4, 52.8, 48.9, 38.3, 21.0, 11.3. IR (KBr disc):

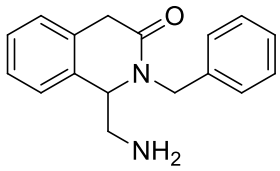
2960, 1733, 1658, 1652, 1436, 1280, 757 cm^{-1}. HRMS (MALDI-FT ICR): *m/z* calcd. for $[C_{17}H_{21}NO_5 + H]^+$: 320.1492; found: 320.1495.

General Procedure for reduction of nitro group. (9)



6a **8**

In a round bottom flask containing the nitro compound **3a** (0.18 mmol), was placed MeOH (1.22 mL), Zinc (0.72 mmol), and then hydrochloric acid (227 µL) was added at 0°C. The mixture was stirred for 25 min and then basified with NaOH. The mixture was filtered and extracted with ethyl acetate. The organic layer was dried with Na_2SO_4 and the solvent removed under reduced pressure. The crude product was purified by chromatography on silica (Chloroform/MeOH, 9:1) affording the corresponding reduction product **(9).**

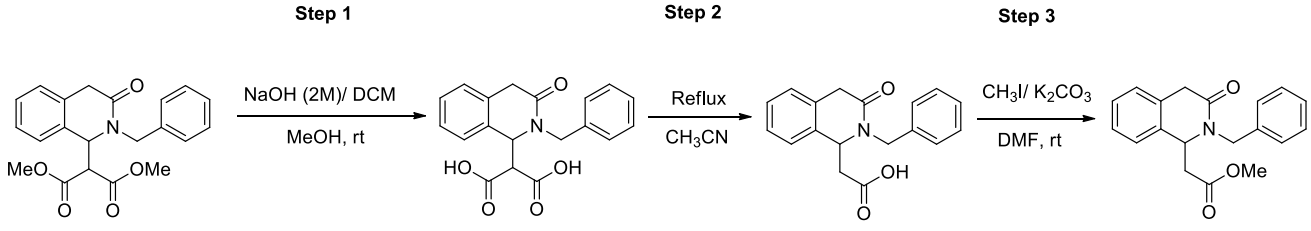


8

1-(aminomethyl)-2-benzyl-1,2-dihydroisoquinolin-3(4H)-one. **(8).**

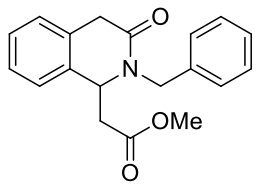
Compound was obtained as a yellow oil in 56% yield (27 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28-7.19 (m, 8H), 7.07 (d, *J= 6.8 Hz*, 1H), 5.39 (d, *J= 15.1 Hz*, 1H), 4.33-4.25 (m, 2H), 3.77 (m, 2H), 2.98 (d, *J= 4.3 Hz*, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7, 137.0, 133.5, 132.6, 128.8, 128.0, 127.8, 127.6, 126.7, 126.2, 77.4, 63.2, 48.6, 45.7, 37.4. IR (KBr disc): 2926, 1652, 1634, 1452, 750 cm^{-1}. HRMS (MALDI-FT ICR): *m/z* calcd. for $[C_{17}H_{18}N_2O + H]^+$: 267.1491; found: 267.1519.

Multistep Procedure for synthesis of monoester analog. (12)



7a **9**

Step 1. In a round bottom flask, the dimethyl ester **7a** (0.21 mmol) was dissolved in DCM (1.0 mL) and a a solution of 2M NaOH in methanol (1.0 mL) wad added dropwise. The mixture was stirred overnight, then the solvent was removed and the residue was taken up with ethyl acetate and acidified with 6M HCl The phases were separated and the aqueous layer was extracted with ethyl acetate (3 x 30 mL). The resulting organic layer was dried with Na_2SO_4 and the solvent removed under reduced pressure affording the crude starting material for the next step. **Step 2**. Compound obtained from Step 1 (0.21 mmol) was solubilized in CH_3CN (1.0 mL) and the mixture was refluxed (oil bath) overnight. The solvent was removed under reduced pressure and the resulting decarboxylated compound was used for the next step without further purification. **Step 3.** Compound obtained from Step 2 (0.11 mmol), was stirred in DMF (1.0 mL)with K_2CO_3 (0.07 mmol) and benzyl bromide (0.12 mmol) for 2h. Then the mixture was diluted with ethyl acetate and washed with water and with brine. The organic layer was dried with Na_2SO_4 and the solvent removed under reduced pressure; purification of the crude by chromatography on silica gel (Hexane/Ethyl acetate, 1:1) affording the final product **9.**



9 ***methyl 2-(2-benzyl-3-oxo-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate*** **(9).** Compound was obtained as a yellow oil in 52% yield (33 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-7.18 (m, 8H), 7.06 (d, *J= 7.7 Hz*, 1H), 5.30 (d, *J= 14.7 Hz*, 1H), 4.84 (dd, J_1*= 5.34 Hz*, J_2*= 2.5 Hz* 1H), 4.24 (d, *J= 14.7 Hz*, 1H), 3.74 (d, *J= 3.3 Hz*, 2H), 3.61 (s, 3H), 2.79-2.57 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 169.7, 136.7, 134.8, 132.0, 128.9, 128.2, 127.9, 127.8, 127.7, 126.9, 125.6, 57.8, 52.1, 48.6, 40.1, 37.5. IR (KBr disc): 2954, 2926, 1734, 1642, 1452, 1437 cm^{-1}. HRMS (MALDI-FT ICR): *m/z* calcd. for $[C_{19}H_{19}NO_3 + H]^+$: 310.1437; found: 310.1466.