University of Szeged

Faculty of Pharmacy

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Doctoral School of Pharmaceutical Sciences

Syntheses and transformation of alicyclic β-amino acid derivatives utilizing conventional and green chemistry methods

PhD Thesis

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2024

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ABBREVIATIONS AND SYMBOLS

ACN	acetonitrile
AcOH	acetic acid
Alum	$KAl(SO_4)_2 \cdot 12H_2O$
BINOL	1,1′-Binaphthalene-2,2′-diol
Bn	benzyl
Boc_2O	di-*tert*-butyl dicarbonate
CF	continuous flow
$CSCl_2$	thiophosgene
CSI	chlorosulfonyl isocyanate
DBSA	dodecylbenzenesulfonic acid
DBTA	(+)-*O,O'*-dibenzoyltartaric acid
DCE	1,2-dichloroethane
DCM	dichloromethane
DIAD	diisopropyl azodicarboxylate
DIC	*N,N'*-diisopropylcarbodiimide
DMAP	dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
DMU	*N,N'*-dimethyl urea
DNP	2,4-dinitrophenol
DPTTA	*O,O*-di-*p*-toluoyltartaric acid
ee	enantiomeric excess
GC	gas chromatography
HDA	hexane-1,6-dioic acid (adipic acid)
HOAc	acetic acid
HOBt	hydroxybenzotriazole
HPLC	high performance liquid chromatography
HPW	phosphotungstic acid
HSBM	high speed ball mill
IPA	isopropyl alcohol
LAG	liquid-assisted grinding
MBIC	(*S*)-α-methylbenzyl isocyanate
MNO-IL-HSO_4	nanomagnetic supported immobilised heterogeneous compound
MW	microwave
NMR	nuclear magnetic resonance spectroscopy
PPh_3	triphenylphosphane
Pt-MWCNTs	multi-walled carbon nanotubes composites
p-TSA	*p*-toluenesulfonic acid
RDA	retro Diels–Alder reaction
rt	room temperature
SA	sulfamic acid
SFC	supercritical fluid chromatography
(*S*)-SPINOL-CPA	(*S*)-2,2',3,3'-tetrahydro-1,1'-spirobi[indene]-7,7'-diol -chiral phosphoric acid
(*S*)-TRIP	(*S*)-3,3′-Bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate
TEA	triethylamine
TFA	trifluoroacetic acid

TLC	thin-layer chromatography
TMSCl	trimethylsilyl chloride
VOC	volatile organic compounds
2M2B	2-methyl-2-butanol, *tert*-amyl alcohol

PUBLICATIONS

Papers related to the thesis

I. Mohamed El Haimer, **Tünde Faragó**, Zsuzsanna Schelz, István Zupkó, Márta Palkó
Synthesis of alicyclic 2-methylenethiazolo[2,3-*b*]quinazolinone derivatives via base-promoted cascade reaction
Synthesis, **2022**, *54*, 3809–3816. (DOI: 10.1055/s-0040-1720028) **IF: 2.6**

II. Sayeh Shahmohammadi, **Tünde Faragó**, Márta Palkó, Enikő Forró
Green strategies for the preparation of enantiomeric 5–8-membered carbocyclic β-amino acid derivatives through CALB-catalyzed hydrolysis
Molecules, **2022**, *27*, 2600. (DOI: 10.3390/molecules27082600) **IF: 4.6**

III. **Tünde Faragó**, Attila M. Remete, István Szatmári, Rita Ambrus, Márta Palkó
The synthesis of pharmacologically important oxindoles via the asymmetric aldol reaction of isatin and the investigation of the organocatalytic activity of new alicyclic β-amino acid derivatives
RSC Advances, **2023**, *13*, 19356–19365. (DOI: 10.1039/D3RA03528J) **IF: 3.9**

IV. **Tünde Faragó**, Rebeka Mészáros, Edit Wéber, Márta Palkó
Synthesis and docking studies of novel spiro[5,8-methanoquinazoline-2,3'-indoline]-2',4-dione derivatives
Molecules, **2024**, *29*, 5112. (DOI: 10.3390/ molecules29215112) **IF: 4.2**

Other papers which not related to the thesis

V. Attila Gácsi, Bence Kutus, Zita Csendes, **Tünde Faragó,** Gábor Peintler, István Pálinkó, Pál Sipos
Calcium L-tartrate complex formation in neutral and in hyperalkaline aqueous solutions
Dalton Transactions, **2016**, *45*, 17296–17303. (DOI: 10.1039/c6dt03463b) **IF: 4.6**

CONFERENCE LECTURES

I. **Faragó Tünde**, Palkó Márta:
Aliciklusos β-aminosav származékok organokatalitikus alkalmazhatóságának vizsgálata: farmakológiailag jelentős oxindolok szintézise izatin aszimmetrikus aldol reakciójával
Szegedi Ifjú Kémikusok Támogatásáért Alapítvány ZOOM konferencia keretében szervezett előadóülése
Szeged, May 25, 2021. (oral presentation).

II. **Tünde Faragó**, Márta Palkó, István Szatmári:
Organocatalytic activity of novel alicyclic β-amino amides in asymmetric aldol reaction
2022 #RSC Poster Twitter Conference
March 1, 2022. (online, poster presentation)

III. Shahmohammadi Sayeh, **Faragó Tünde**, Palkó Márta, Forró Enikő:
Green enzymatic strategies for the preparation of enantiomeric carbocyclic β-amino acid derivatives
4th International Green Catalysis Symposium, GreenCat
Rennes/France, April 19–22, 2022. P6 (poster presentation)

IV. **Faragó Tünde**, Palkó Márta, Szatmári István:
Változatosan szubsztituált enantiomertiszta aliciklusos β-aminosav-származékok szintézise és organokatalitikus alkalmazhatóságának vizsgálata izatin aszimmetrikus aldol reakciójával
MTA Heterociklusos és Elemorganikus Kémiai Munkabizottság ülése,
Balatonszemes, May 23–25, 2022. (oral presentation)

V. Márta Palkó, **Tünde Faragó**, István Szatmári:
Synthesis of glycosyl triazolyl methanopyrroloquinazoline and methanoisoindoloquinazoline derivatives via domino- and click reactions
22nd Tetrahedron Symposium
Lisbon/Portugal, June 28–July 1, 2022. Abstract reference number: 188, P2.27 (poster presentation)

VI. **Tünde Faragó**, Márta Palkó, István Szatmári:
Novel alicyclic β-amino amide organocatalysts for the synthesis of pharmaceutically relevant oxindoles
22nd Tetrahedron Symposium
Lisbon/Portugal, June 28–July 1, 2022. Abstract reference number: 198, P2.36 (poster presentation)

VII. **Faragó Tünde**:
Aliciklusos β-aminosav származékok előállítása és organokatalitikus alkalmazhatóságának vizsgálata: farmakológiailag jelentős oxindolok szintézise izatin aszimmetrikus aldol reakciójával
MTA Heterociklusos és Elemorganikus Kémiai Munkabizottságának a Patonay Tamás-díj átadásával egybekötött nyílt ülése
Budapest, November 25, 2022. (oral presentation)

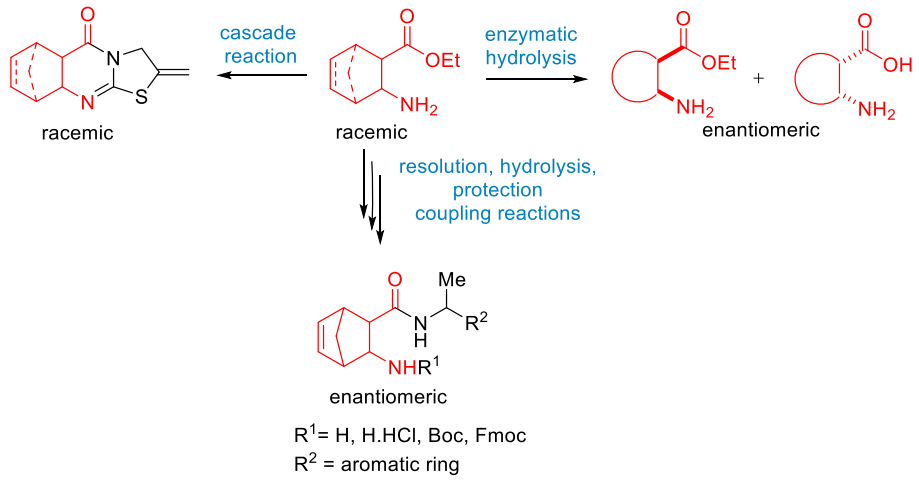
VIII. **Tünde Faragó**, Márta Palkó:
Synthesis of novel spiro[5,8-methanoquinazoline-2,3'-indoline]-2',4-dione derivatives starting from alicyclic β-amino amides
23nd Tetrahedron Symposium
Gothenburg/Sweden, June 27–30, 2023. Abstract reference number: TETR2023_0366, P3.001 (poster presentation)

IX. **Tünde Faragó**, Márta Palkó:
Synthesis and docking studies of novel spiro[5,8-methanoquinazoline-2,3'-indoline]-2',4-dione derivatives
#RSC Poster Conference 2024 Linkedin
March 5, 2024. (online, poster presentation)

1. INTRODUCTION AND AIMS

The synthesis of natural compounds is a huge challenge for scientists. Numerous diverse natural products have the oxindole or dihydroquinazoline core and these compounds own a significant scientific attention thanks to their wide range of biological activities. For example, arundaphine, convolutamydines, maremycins and CPC-1 have biological features, such as antioxidative, anti-HIV and neuroprotection activity [1–6]. Recently, there has been a considerable interest in developing more sustainable synthetic pathways for pharmacologically relevant derivatives [7,8]. Because of the importance of a sustainable future in today's world, green chemistry is becoming desirable and more and more attractive. There is still a need for new, environmentally benign and effective catalytic systems for the preparation of organic compounds in pharmaceutical chemistry. Dihydroquinazolinone derivatives, which have attracted the interests of researchers recently, have important biological activities like antitumor and anticancer effects [9]. Synthesis of different kinds of dihydroquinazolinone compounds and finding greener synthetic procedures to obtain this kind of derivatives requires on-going development.

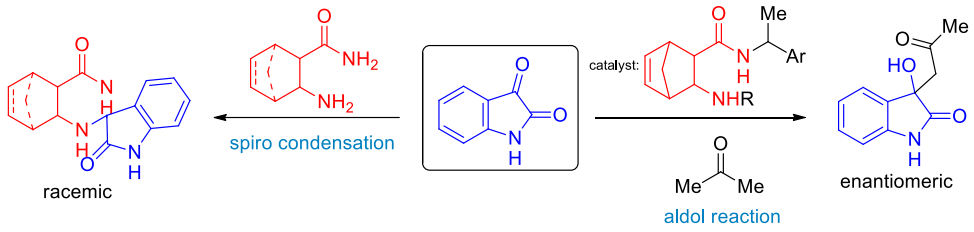
In view of the growing importance of β-amino acid derivatives [10–15], the first aim of my PhD work was to develop a simple route for the synthesis of 2-methylenethiazolo-[2,3-*b*]quinazolinone derivatives. Another goal was to expand efficient strategies for the enzymatic resolution of 5–8-membered alicyclic amino esters through hydrolysis in green organic media, under solvent-free conditions and using ball milling. We have achieved the syntheses of enantiomers of 2-aminocycloalkanecarboxylic acid and ester derivatives starting from the appropriate racemic esters (Scheme 1).



Scheme 1

An additional aim was to examine greener synthetic procedures and the organocatalytic applicability of the alicyclic β-amino acid derivatives. Testing the catalytic applicability of substituted enantiomeric alicyclic β-amino amides in the asymmetric aldol reaction of isatin and acetone was also amongst our intentions.

By spiro-condensation reactions of isatin and alicyclic β-amino amides the synthesis of racemic tetrahydro-1*H*-spiro[5,8-methanoquinazoline-2,3'-indoline]-2',4-dione derivatives was targeted (Scheme 2).



Scheme 2

The significance of β-amino acid derivatives was previously described in the literature in reviews [16,17]. For that reason, introducing the literature background will be focused on the reactions of β-amino acid derivatives with isatin and its derivatives and other compounds closely connected to these compounds, which are tightly related to my PhD work.

2. LITERATURE BACKGROUND

Isatin, commonly known as tribulin, is an indole derivative (2,3-dioxindole, 1*H*-indole-2,3-dione). It is a tiny yet flexible chemical building block that can participate in a wide range of synthetic processes (Figure 1). Isatin derivatives are a class of heterocyclic chemicals that can be used to synthesise various heterocyclic structures such as oxindoles and spirooxindoles, as well as fused compounds [18].

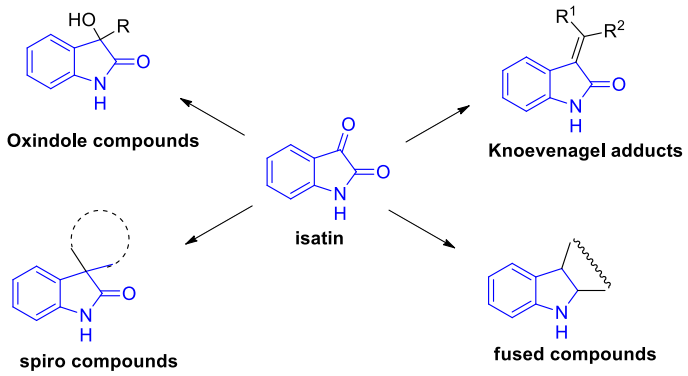


Figure 1

Compounds, such as spirotryprostatin A and B, elacomine and rhynchophylline containing the spirooxindole skeleton, have been found to possess antitumor effects. Therefore, they have attracted scientists as anti-cancer drugs (Figure 2) [9, 19,20].

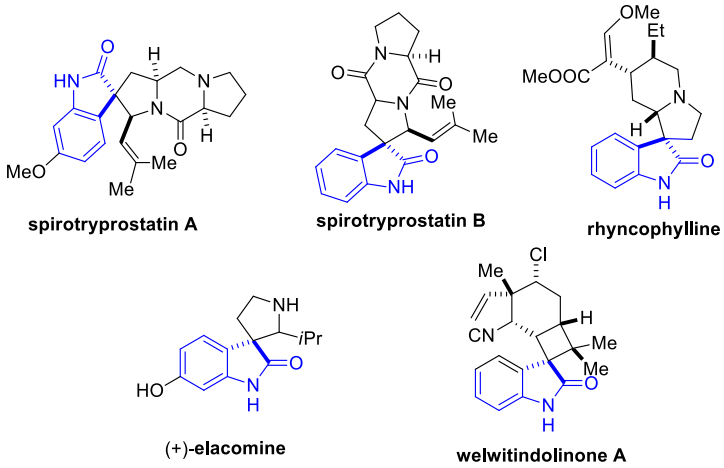
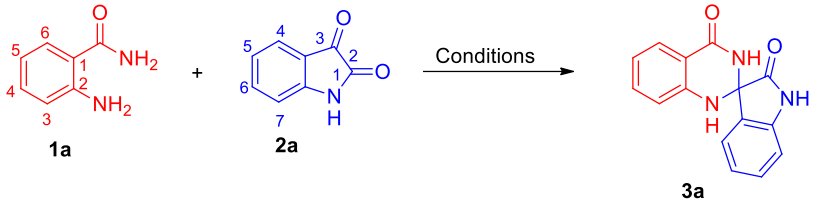


Figure 2

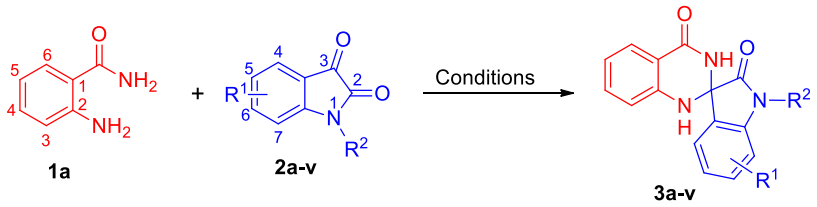
2.1. Reactions of isatins with 2-amino benzamides

In the last two decades the topic of the synthesis of 2,3-dihydroquinazoline-4-ones and oxindole derivates attracted the attention of scientists. The first known synthesis of racemic spiro[isoindoline-1,2'-quinazoline]-3,4-dione **3a** were published by Shaabani et al. and Dabiri an co-workers in 2008 [21,22]. It was obtained by the spirocyclization reaction of 2-aminobenzamide **1a** and isatin **2a** (Scheme 3).



Scheme 3

Various substituted isatins were tested in this condensation reaction resulting in the corresponding racemic spiro products **3a**–**v**. A few examples of substituted isatins are *N*-methylisatin **2b**, 5-methylisatin **2c**, 5-methoxyisatin **2d**, *N*-propargylisatin **2e**, 5-fluoroisatin **2f**, 5-chloroisatin **2g**, 5-bromoisatin **2h** and 5-nitroisatin **2i**, etc. (Scheme 4) [21–32].



a: R^1= H, R^2= H, **b**: R^1= H, R^2= Me, **c**: R^1= 5-Me, R^2= H
d: R^1= 5-MeO, R^2= H, **e**: R^1= H, R^2= propargyl **f**: R^1= 5-F, R^2= H
g: R^1= 5-Cl, R^2= H, **h**: R^1= 5-Br, R^2= H, **i**: R^1= 5-NO_2, R^2= H
j: R^1= 5-I, R^2= H **k**: R^1= H, R^2= Bn **l**: R^1= 5,6-diMe, R^2= H
m: R^1= 4-F, R^2= Bn **n**: R^1= 5-Cl, R^2= Bn **o**: R^1= 6-Cl, R^2= Bn
p: R^1= 6-Br, R^2= Bn **q**: R^1= 7-Me, R^2= Bn **r**: R^1= 6-Br, R^2= Me
s: R^1= 6-F, R^2= Bn **t**: R^1= 7-CF_3, R^2= Bn **u**: R^1= 7-Me, R^2= Bn
v: R^1= 7-Br, R^2= Bn

Scheme 4

Many research groups have examined the spirocyclization process in the nearly two decades since then. Different types of catalysts, solvents and temperatures were applied in order to obtain racemic compounds **3a**–**l** (Table 1) and enantiomeric derivatives **3a** and **3m**–**v** (Table 2) [21–32].

Table 1 Condensation reaction of **1a** and **2a–l** to obtain racemic spirooxindoles **3a–l** investigated under varied conditions.

Catalyst	Conditions	Products	Literature
NH_4Cl	EtOH, rt, 1 h	**3a**	Shaabani et al. 2008[21]
Alum ($KAl(SO_4)_2*12H_2O$)	EtOH, reflux, 7 h	**3a**	Dabiri et al. 2008[22]
p-Toluenesulfonic acid *(p*-TSA)	EtOH, reflux, 1 h	**3a**, **3g**, **3i**	Lalitha et al. 2015[23]
Sulfamic acid (SA)	EtOH, rt, 40 min	**3a**, **3c**, **3d**, **3f–h**	M. Pore et al. 2016[24]
nanomagnetic supported immobilised heterogeneous compound (MNO-IL-HSO_4)	EtOH, rt, 125 min	**3a**	Fallah-Mehrjardi et al. 2020[25]
Rose Bengal photo catalyst	EtOH, rt, 2 h	**3a**, **3c**, **3g–l**	Kovvuri et al. 2020[26]
Cellulose SO_3-H	MeCN, rt, 50 min	**3a**	Reddy et al. 2011[27]
Amberlyst 15	MeCN, rt, 3 h	**3e**	Pal et al. 2013[28]
-	AcOH, visible light irradiation	**3a**	Madhumitha et al. 2015[29]
50w/w% HPW	solvent free, MW 200 W, 3 min	**3a**, **3b**	Kannadasan et al. 2019[30]
-	deep eutectic solvent (DES) mixture: L-Tartaric acid: DMU 3:7,	**3a**	Nagarajan et al. 2016[31]
-	Glycerin, 80 °C, 3 min	**3a**	Lalitha et al. 2017 [32]

Shabaani et al. published an easy method for the synthesis of **3a**. First NH_4Cl was added to the stirred solution of **1a** and **2a** in EtOH at room temperature. Product **3a** was precipitated by adding water and then; after washing with water, the residue was crystallised from acetone. [21]. Dabiri and his co-workers used alum as catalyst and purified the crude product similar to that by Shabaani et al. and **3a** was isolated in an excellent yield of 92% [22]. Researchers also performed reactions in EtOH using different acidic catalysts, for example *p*-TSA, sulfamic acid or nanomagnetic immobilised heterogeneous compounds (MNO-IL-HSO_4) [23–25]. Rose Bengal photocatalyst was applied by Kovvuri et al. in EtOH under mild conditions. They extended their research by using a variety of substituted isatins **2g**–**l** and obtained the

corresponding pure products with moderate to good yields (45–91%) [26]. Reddy et al. and Pal and co-workers performed the reaction in MeCN at room temperature utilizing cellulose-SO_3-H, a biodegradable solid and Amberlyst 15 as catalysts under ultrasonic irradiation [27,28]. Madhumitha and his co-workers discovered a solvatochromic effect during the photochemical synthesis of a series of 2,3-dihydroquinazolin-4(1*H*)-ones [29]. The synthesis of the target compounds was tested under visible light irradiation in the presence of solvents or under solvent-free conditions. They found that the solvent has a significant impact on product formation in short terms. They examined solvatochromic effects of fluorescent compounds with increasing polarity (DCM < MeOH< DMF < DMSO) [29]. Kannadasan et al. used phosphotungstic acid, a heterogeneous green solid acid catalyst under solvent-free conditions and MW irradiation [30]. According to their investigation, increasing the catalyst load between 20–100 w/w% better results in yield could be obtained, while decreasing the catalyst load did not change the yield. Consequently, a catalyst loading of 50 w/w% was found to be optimal. Note, however, that it is still a high amount [30]. Nagarajan et al. published a green protocol to synthesise quinazolinone derivatives via cyclization with a series of aldehydes and ketones mediated in a deep eutectic solvent (DES) in good to excellent yields of 62–95% [31]. To generate quinazolinone derivatives, the authors began by optimizing several deep eutectic solvent mixes. Among them, the mixture of L-(+)-tartaric acid and *N*,*N*'-dimethylurea (DMU) (3:7) melting at 90 °C was found to be the most effective to give the maximum yield of derivative **3a**. The reaction was carried out in an open-air atmosphere. Lalitha et al. stirred the mixture of starting materials and glycerol at 80 °C for 3 minutes affording product **3a** in a good yield of 90% [32]. Neither Nagarajan nor Lalitha used any other catalyst. The syntheses of enantiomers or enantiomeric mixtures of dihydroquinazolin-4-one derivatives using chiral catalysts or chiral environments are collected in Table 2.

Table 2 Condensation reaction of **1a, 2a, 2m**–**v**, *N*-substituted anthranilic amide and isatins to obtain enantiomeric spirooxindoles, investigated under varied conditions.

Catalyst	Conditions	Enantiomers of product	*ee* (%)	Literature
(*S*)-TRIP Chiral phosphoric acid derivative	Toluene, 5 Å MS, 70 °C, 4 h	**3a**	84	List et al. 2008[19]
(*S*)-TRIP Chiral phosphoric acid derivative	DCE, 30 °C, 5 Å MS	**3a, 3m**–**v**	52–86	Shi et al. 2013[33]

Table 2 Condensation reaction of **1a, 2a, 2m**–**v**, *N*-substituted anthranilic amide and isatins to obtain enantiomeric spirooxindoles, investigated under varied conditions.

Catalyst	Conditions	Enantiomers of product	*ee* (%)	Literature
SPINOL-CPA Chiral phosphoric acid derivatives	additive, DCM, 30 °C	**3b, 3k, 3o, 3α–3ψ**	70–99	Zuo et al. 2018[34]
Chiral imidazoline-phosphoric acid 10 mol%	DCE, rt, 168 h	**3k**	91	Nakamura et al. 2020[35]

In 2008 List and his co-workers developed the direct synthesis of chiral spirocyclic product **3a** from isatin using (*S*)-TRIP (**I**) as catalyst (Figure 3). (*S*)-TRIP (**I**, 10 mol%) in toluene (70 °C, 4 h) and 5 Å molecular sieve as additive were used and the enantiomer of **3a** was isolated in a good yield of 85% with an *ee* > 84%. The *ee* value was determined by HPLC, but the authors did not give the absolute configuration of the major enantiomer [19].

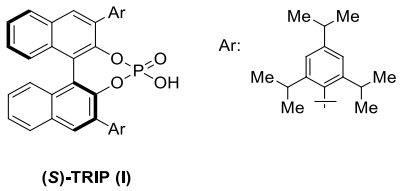
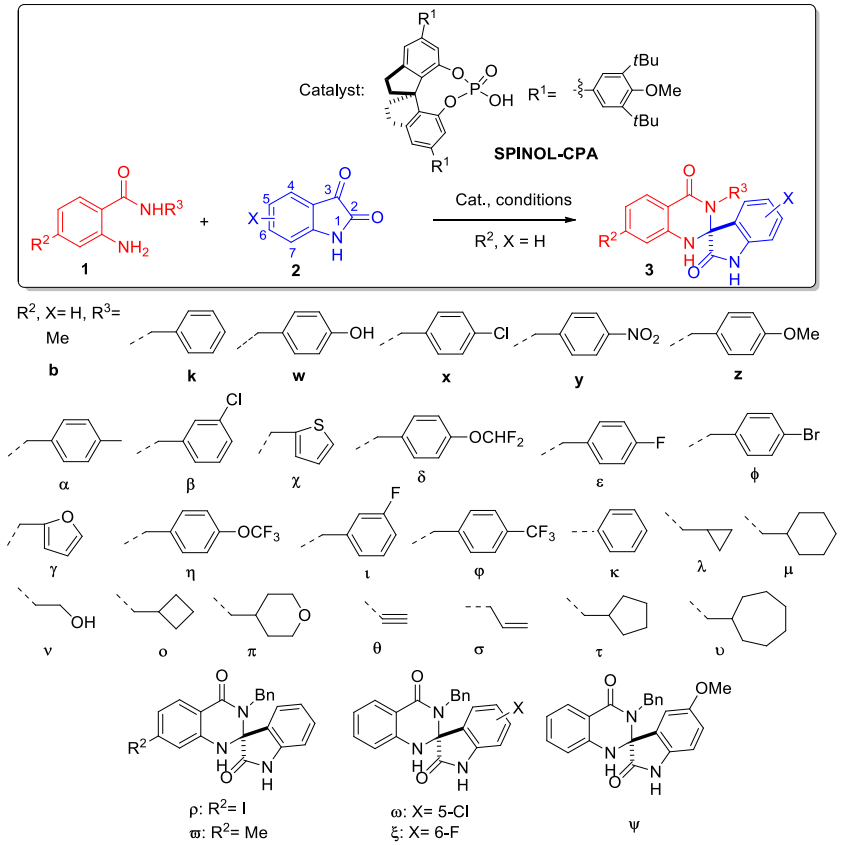


Figure 3

Ten years ago, Shi et al. utilised the same chiral phosphoric acid catalyst ((*S*)-TRIP, **I**) containing triisopropylphenyl groups at the 3,3′-positions of the BINOL backbone (10 mol%) in DCE and in the presence of a molecular sieve and they isolated the enantiomers of **3a** in good yield (95%) with a 72% *ee*. This method was applicable to mono- or di-substituted 2-aminobenzamides with various substituents, including electron-donating and electron-withdrawing groups, yielding the desired **3a**, **3m**–**v** spiro[indoline-3,2′-quinazolines] with 52–86% *ee*. The absolute configuration of the 6-Br- and *N*-Bn-substituted derivative **3p** was determined by X-ray analysis using a single crystal [33].

A variety of enantiomeric 3-*N*-substituted spirooxindole-dihydroquinazolinones was synthesised in a highly enantioselective manner using *N*-substituted anthranilic amide and isatins catalysed by SPINOL-CPA catalyst with excellent *ee* values (up to 99%) and good yields (up to 99%) by Zuo et al. This protocol was the first example of the direct access of chiral,

pharmaceutically privileged 3-*N*-substituted dihydroquinazolinone derivatives **3b**, **3k**, **3o** and **3α–3ψ** with a broad substrate scope [34] (Scheme 5).



Scheme 5

Nakamura et al. utilised chiral bis(imidazoline)-phosphoric acid catalysts (**II**) (Figure 4) in DCE in the reaction of 2-aminobenzamide **1a** and *N*-benzylisatin **2k** at room temperature and isolated the product in excellent yield (94%) and *ee* (91%) [35].

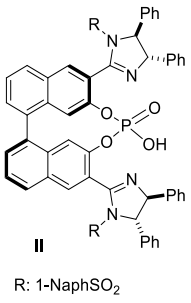


Figure 4

Bergman et al. obtained racemate product **3a** with 88% yield but the separation of the enantiomers was only successful with supercritical fluid chromatography (SFC) [36]. They

measured the optical rotation of the **3a** enantiomers ([α] = –210 and [α] = +248) and observed their rapid racemization [19,36].

2.2. Asymmetric aldol reaction of isatins with ketones

Oxindole-containing compounds are found in a wide variety of natural products. In addition, there is a substantial interest due to a wide range of biological activities that interest scientists including chemists, pharmacists and biologists (Figure 5) [1,2].

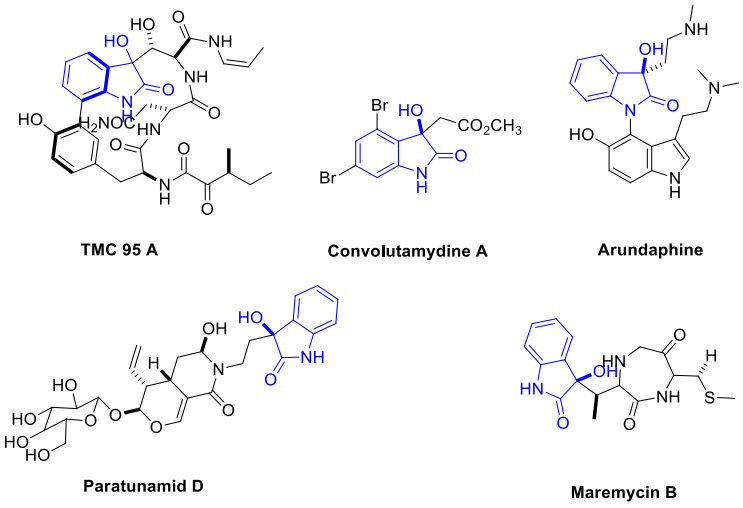
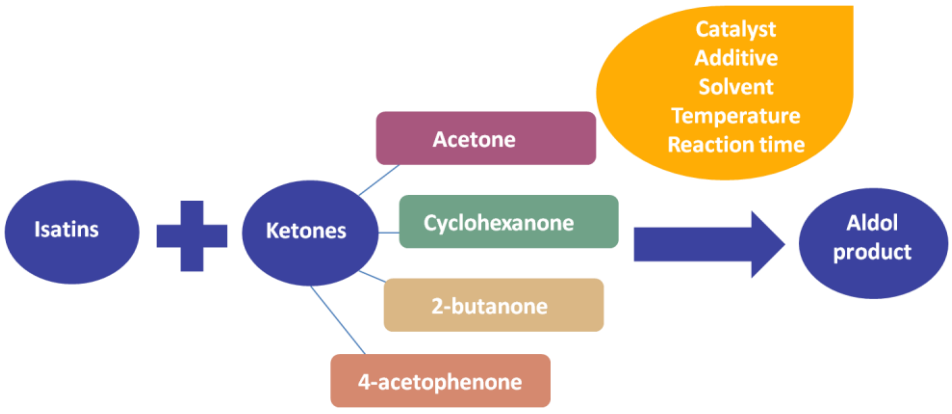


Figure 5

Many scientists chose the aldol condensation of isatins and ketones as model reaction, for studying and optimizing the synthesis of pharmaceutically relevant compounds with the oxindole moiety [2,37–40]. Isatin and its substituted derivatives are usually used in the aldol reaction with ketones, for example, 2-butanone and 4-acetophenone, but acetone and cyclohexanone are most commonly applied reactants (Scheme 6) [37–43].



Scheme 6

Various parameters such as catalyst, co-catalyst, catalyst loading, additive, solvents, reaction time and temperature can have an impact on the aldol reaction (Scheme 6). Different types of

catalysts were developed to obtain the aldol product in better yields and *ee*. It was discovered, that good results can be obtained when small organic molecules are used as catalysts in chemical reactions, including enantioselective synthesis [8]. In addition, catalytic efficiency and catalyst loading have a huge impact on asymmetric reactions. In comparison to enzyme or metal catalysis, organocatalysis has various advantages. Among other features, they are less hazardous and they work with low catalyst loadings. Furthermore, they do not require special containers or atmosphere, they are cheap and they can be applied on a small to industrial scale [8]. Three decades ago, catalyst loading in organocatalytic reactions was about 20–30 mol% but recently, the main goal is to use less than 5–10 mol% catalyst amount [42]. Within the field of organocatalysis, catalytic procedures of aminocatalysis, predominantly proline and connected secondary amines, were tested [37,44,45]. The most examined types of primary and secondary amines are represented on Figure 6 [37].

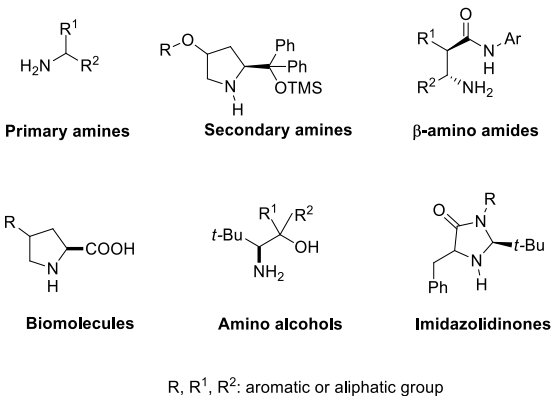


Figure 6

Based on their bonding features, organocatalysts can be grouped into diverse categories such as bonds of covalent and non-covalent types (hydrogen bond and electrostatic ion pairs) (Figure 7) [46].

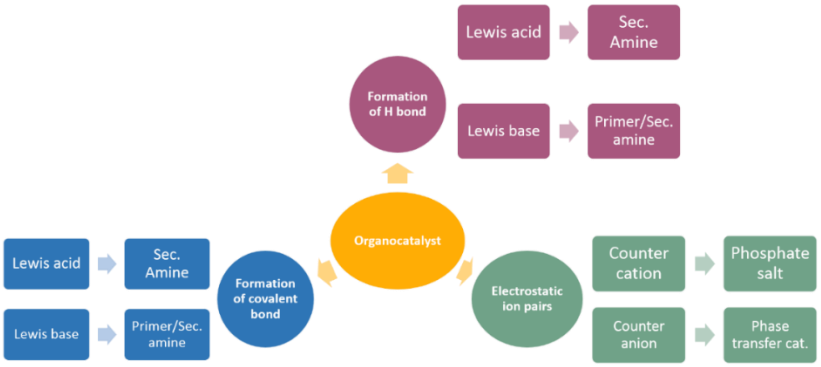
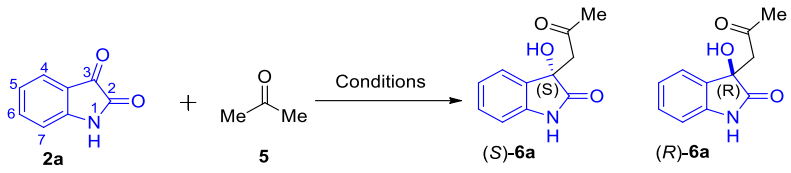


Figure 7

The asymmetric aldol reaction of isatin and acetone forming two enantiomeric aldol products was already thoroughly studied in the last two decades (Scheme 7) [2,3,37,38,40,42,47–55].



Scheme 7

There are publications in the literature exploring the influence of distinct conditions including the type of catalysts, the amount of compounds used, additives, effects of solvents, temperature and reaction time (Table 3) [2,3,37,38,40,42,47–55].

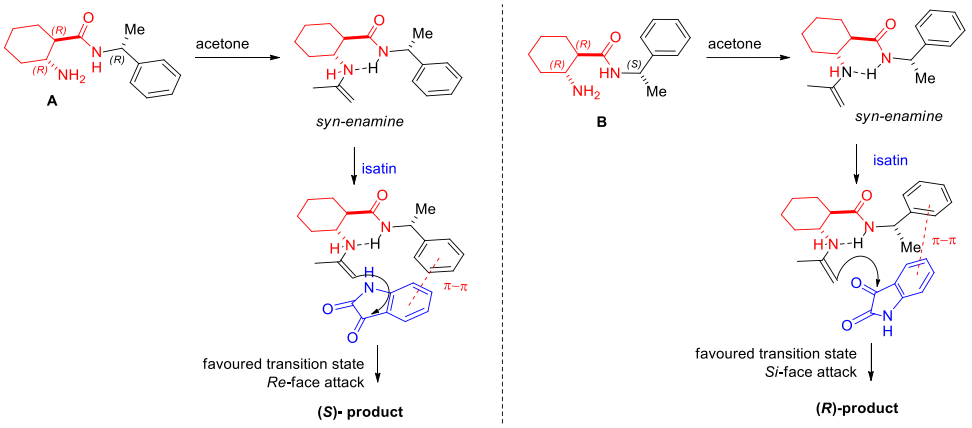
Table 3 Asymmetric aldol reaction of **2a** and **5** to obtain **6a** investigated under varied conditions.

Catalyst	Cat. (mol%)	Conditions	config. *ee* (%)	Literature
prolinamide derivatives	20	additive 20 mol%, –20 °C, 15–312 h	*S* 58–72	Lennon et al. 2011[2]
heteroarylsulfonylprolinamides	5	H_2O, 0 °C, 24 h	*R* 51–96	Nakamura et al. 2008[3]
alicyclic β-amino amides	20	additive, EtOH, rt 24–96 h	*S* 34–48	Kinsella et al. 2019[37]
prolinamide	10	THF, rt or –35 °C, 48 h	*S* 36–74	Singh et al. 2016[38]
L-proline-derived bifunctional organocatalyst	10	AcOH 20 mol%, 35 °C, 3–90 h	*S* 61–81	Xiao et al. 2007[47]
Li salt of amino acid	20	solvent, rt, 12–84 h	*S* 15–49	Li et al. 2015[42]
vicinal diamines	10	THF, dioxane, 5 °C, 2–8 days	*S* 46–90	V.K. Singh et al. 2011[48]
[2,2] paracyclophane based amino thioureas	20	H_2O, THF, rt, 48–96 h	*S* 15–68	Song et al. 2013[50]
primary-tertiary BrØnsted acid conjugate diamines	1	DNP 1 mol%, water, rt, 24 h	*R* 62–80	Chimni et al. 2013[51]
dipeptide	10	–15 °C, 20 °C, 15–64 h	*S* 20–46 *R* 4–73	Tomasini et al. 2005[52]
chiral 2-aminopyrimidin-4(1*H*)-ones	20	THF, rt, 3–13 days	*R* 71–80	Ren et al. 2015[53]
(*R*,*R*)-*o*-phenylenediamine	20	THF, EtOH, additive H_2O, 10 °C 3–4 days	*R* 53-91	Guan et al. 2017[54]

Table 3 Asymmetric aldol reaction of **2a** and **5** to obtain **6a** investigated under varied conditions.

Catalyst	Cat. (mol%)	Conditions	config. *ee* (%)	Literature
vicinal amino alcohols, leucinol	10–20	acetone, DCM, rt, 36 h	*S* 70–98	Malkov et al. 2007[40]
carbohydrate-derived alcohols	10	DCM, 0 °C, 1–4 days	*S* 25–67	Chen et al. 2011[49]
L-leucinol	20	additives, solvents, 20 °C, 48 h	*S* 33–93	Kinsella et al. 2021[55]

Lennon et al. examined the catalytic activity of prolinamide derivatives with 20 mol% catalyst at –20 °C and the reactions required longer treatments. They also optimised the reaction conditions and proposed a relationship between the pKa value of acidic additives and yield and *ee* of the products. It was intriguing that the curve of pKa versus enantioselectivity showed much similarity with a pH titration curve. Hence, a pKa value of approximately 4.0–6.0 was proposed to be appropriate of the acid additive considering both yield and enantioselectivity [2]. Nakamura et al. studied the catalytic effect of 5 mol% TFA salts of *N*-heteroarylsulfonylprolinamides as catalyst at 0 °C in the presence of H_2O [3]. Kinsella and his colleagues applied alicyclic β-amino amides originating from rare unnatural β-amino acid scaffolds at room temperature [37]. They also screened various additives in an amount of 20 mol% such as *p*-TSA, TFA, HCOOH, AcOH, *p*-nitrophenol, *m*-nitrophenol, phenol, MeOH and H_2O, iPrOH in order to enhance the catalytic performance of their compounds. Furthermore, the possible effects of used solvents were investigated through testing different kind of solvents such as EtOH, MeOH, H_2O, brine, iPrOH, THF, CH_2Cl_2, ACN, DMSO, Et_2O, toluene and cyclohexane. Their best condition was observed with the application of 20 mol% catalyst in ethanol in the presence of *p*-nitrophenol at room temperature when (*S*)-3-alkyl-3-hydroxyindolin-2-one afforded a good yield of 95% but with a moderate *ee* value (48%). A mechanistic study was also performed. They suggested that by *Re*-face attack resulted in the (*S*)-aldol product with one of best working catalyst **A**. In contrast, the other catalyst **B** afforded the (*R*)-product through *Si*-face attack (Scheme 8).



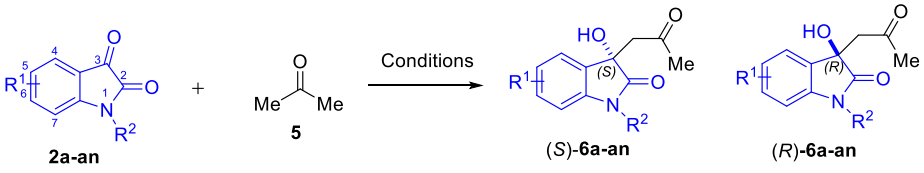
Scheme 8

Singh and his colleagues tried *trans*-4-hydroxy-L-prolinamide as catalyst in the aldol reaction and obtained the product with moderate to good *ee* values [38]. Xiao et al. utilised L-pyroglutamic acid-derived bifunctional organocatalyst in the presence of AcOH (20 mol%) at 10 °C isolating the product in excellent yield but good *ee* [47]. Li et al. examined the lithium salt of phenylalanine under milder conditions and had the product in moderate *ee* without optimization of the conditions [42]. Furthermore, Singh et al. examined vicinal diamines as catalysts at 5 °C in unusually long reactions (several days). They proposed a mechanism for the aldol reaction with 4,6-dibromo-isatin (see next page, Scheme 9, **2aa**) in which a *Si*-face attack was favoured [48]. Song and colleagues investigated amino thiourea derivatives as catalysts in the aldol reaction, using H_2O as additive and THF as co-solvent at room temperature. They isolated the (*S*)-products after 48 hours in low-to-moderate *ee* values [50]. Chimni and Kumar applied primary–tertiary diamines as catalysts (1 mol%) and 2,4-dinitrophenole (1:1, H_2O as solvent, 24 h) to have the aldol compounds [51]. Tomasini et al. examined dipeptides as organocatalysts at –15 °C and 20 °C with 10 mol% loading to synthesise the (*S*) and (*R*) enantiomer aldol products in moderate *ee* [52]. In addition, Ren and his co-workers investigated the catalytic applicability of chiral 2-aminopyrimidin-4(1*H*)-one derivatives in THF, at room temperature, which resulted in the aldol products in good *ee*, but rather long reactions (3–13 days) [53]. Similar to the previously examined diamine catalysts, Guan et al. investigated chiral phenylenediamine catalysts at 10 °C in THF and EtOH. The catalysts proved their effect after four days and resulted in the formation of the (*R*)-aldol products in good *ee* [54]. Their best condition was 20 mol% catalyst loading, at 10 °C with 10 μL H_2O as additive after three days they got the (*R*)-enantiomer in 91 % *ee*.

The catalytic activity of amino alcohols was examined by Malkov et al. in 2007, Chen et al. in 2011 and Kinsella and co-workers in 2021. All of them utilised 10–20 mol% catalyst with DCM as additional solvent affording the (*S*)-aldol compounds in moderate to good *ee* values [40,49,55].

In general, mainly primary and secondary amine derivatives as well as amino alcohols were used as catalyst in the literature so far. As far as the amount of organocatalyst is concerned, it was used in a large range from 1, 5 and 10–20 mol%. The applied solvents included mostly H_2O, THF, DCM, EtOH or acetone without using any other solvents in the aldol reaction of **2a** and **5**. The use of additives with acidic characteristics included, among others, *p*-TSA, TFA, HCOOH, 4-nitrophenol and AcOH. Regarding the temperature, milder conditions, such as room temperature, were dominant in studies, but examples for application of –35 °C, –15 °C, 0 °C, 10 °C and 20 °C can also be found. Despite utilising catalysts, additives and other possibilities to enhance the catalytic performance, reaction times were rather long, e.g. 96–168 h, whereas very good *ee* values were reported in just a few cases.

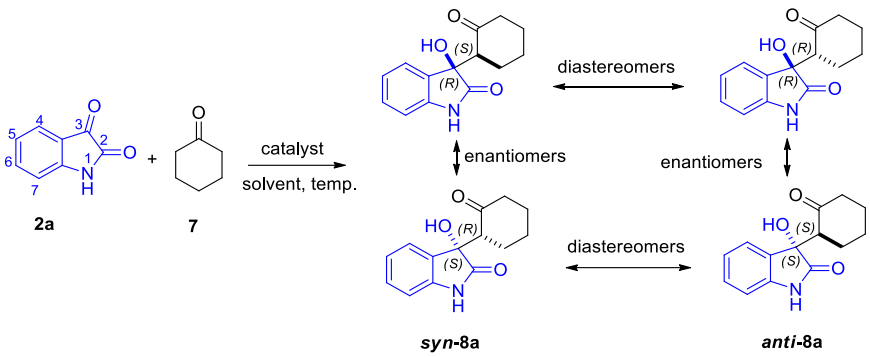
When substituted isatins were screened in the aldol reaction with acetone, better results were obtained in most cases in comparison with isatin itself. Diverse substituents like fluoro, chloro, bromo, iodo, nitro, propargyl or benzyl group in different positions of the isatin ring, such as C–4, C–5, C–6, C–7 or the nitrogen atom of the five-membered ring of isatin were widely utilised in the literature in the aldol reaction of **2a**–**an** and **5** (Scheme 9) [38,43,50–55].



a: R^1= H, R^2= H, **b**: R^1= H, R^2= Me, **c**: R^1= 5-Me, R^2= H
d: R^1= 5-MeO, R^2= H, **e**: R^1= H, R^2= propargyl **f**: R^1= 5-F, R^2= H
g: R^1= 5-Cl, R^2= H, **h**: R^1= 5-Br, R^2= H, **i**: R^1= 5-NO_2, R^2= H
j: R^1= 5-I, R^2= H **k**: R^1= H, R^2= Bn **l**: R^1= 5,6-diMe, R^2= H
aa: R^1= 4,6-diBr, R^2= H **ab**: R^1= 4,6-diF, R^2= Bn **ac**: R^1= 4,6-diCl, R^2= H
ad: R^1= 7-CF_3, R^2= H **ae**: R^1= 4-F, R^2= H **af**: R^1= 4-Cl, R^2= H
ag: R^1= 4-Br, R^2= H **ah**: R^1= 4-Me, R^2= H **ai**: R^1= 6-Cl, R^2= H
aj: R^1= 7-Cl, R^2= H **ak**: R^1= 4,7-diCl, R^2= H **al**: R^1= 5,7-diCl, R^2= H
am: R^1= 7-F, R^2= H **an**: R^1= 6-Br, R^2= H

Scheme 9

It is worth to mention the aldol reaction of isatin **2a** and cyclohexanone **7**. Product **8a** has two chiral centres (Scheme 10) and, therefore, two diastereomers (*syn* and *anti*) can be formed in the aldol reaction of these compounds. Related dr and *ee* values are collected in Table 4.



Scheme 10

Research groups studied the aforementioned reaction under various conditions (Table 4) [40,41, 53, 56–60].

Table 4 Asymmetric aldol reaction of **2a** and **7** to obtain **8a** investigated under varied conditions.

Catalyst	Catalyst loading mol%	Conditions	dr (*syn:anti*) *ee* (%)	Literature
2-azanorbornane-based amines	20	TFA 10 mol%, toluene, rt,72 h	36:64 64	Nakano et al. 2016[39]
primary-tertiary Brønsted acid conjugate organocatalyst	1	HDA 20 mol%, MeOH:H_2O 1:1, rt	1:20 99	Li et al. 2012[41]
primary amino acid derived sulfonamides	20	4Å MS, $CHCl_2$, rt, 24 h	95:5 92	Yang et al. 2015[56]
prolin-glycine dipeptidic derivatives of chiral phosphoramides	10	water, 3 °C, 48 h	20:80 92	Juaristi et al. 2018[57]
(*R*) and (*S*) prolin derived chiral phosphoramides	10	water, 3 °C or 25 °C, 48 h	20:80 77	Juarist et al. 2018[58]
L-pyroglutamic acid derivative	20	DMF, rt, 6 h	1:20 95	Chen et al. 2018[59]
chiral bifunctional primary amin organocatalyst	10	H_2O, rt, 48 h	98:2 99	Du et al. 2023[60]

Nakano et al. used 2-azanorbornane-based amines and 20 mol% catalyst with 10 mol% of TFA utilised as additive in toluene at room temperature [39]. Compound **8a** was isolated in a good yield but with a poor *ee* 64% and dr 36:64 [39]. Li et al. applied 20 mol% of primary 1,2 diamine added with 20 mol% HDA in a 1:1 mixture of methanol and water at room temperature. After the completion of the reaction, the product was obtained in excellent *ee* (99%) and dr (1:20). Substituted isatins gave products with slight decreases in *ee* values [41]. Yang et al. investigated sulfonamides as catalyst derived from primary α-amino acids under neat conditions. The sulfonamide catalyst derived from alanine worked especially well and they used chiral HPLC

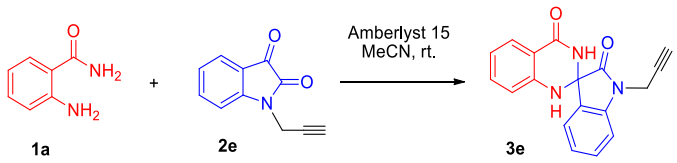
analysis [56]. Juaristi et al. utilised proline–glycine dipeptide derivatives of chiral phosphoramides in the reaction between isatin and cyclohexanone at 3 °C. The reaction took 48 hours and the authors determined the structure of their possible intermediate by X-ray diffraction crystallographic analysis [57]. In a subsequent publication by the Juaristi group, the aldol reaction of isatins was examined with use of chiral phosphoramides derived from (*R*)- and (*S*)-proline in the presence of H_2O at room temperature and 3 °C. They had the same good results similar to those in their previous publication [58]. Chen and colleagues in 2018 studied the catalytic effect of a bifunctional organocatalyst derived from L-pyroglutamic acid at room temperature [59]. They suggested that a stereospecific retro-aldol reaction could be responsible for erosion in *ee* values during the aldol reaction between isatin and ketones. Du et al. examined bifunctional chiral primary amine organocatalysts in water at room temperature and obtained the product in excellent dr and *ee* without column chromatography, because product the remains in the aqueous phase [60].

2.3. Application of environmentally benign methods for the synthesis of oxindole and 2,3-dihydroquinazoline-4-one derivatives

In recent decades, developing more sustainable synthetic procedures is of increasingly interest. Reasons behind this phenomenon involve less toxicity, simplicity, less waste-producing ability, safer usage, lower cost and better energy effectiveness. The main aim of green chemistry is to develop environmentally benign, more effective and, at the same time, more selective organic syntheses. In the field of organic chemistry several research groups created environmentally benign synthesis routes to access pharmacologically valuable compounds. The aforementioned green or greener reaction routes include the field of asymmetric organocatalysis. Small organic molecules, for example amino acids, are used as catalysts in order to develop more sustainable asymmetric reactions and to enhance selectivity [8]. Regarding asymmetric synthesis, alternative methods such as the use of ionic liquids, CF reactor, ultrasound irradiation, MW irradiation and high-speed ball milling were tested. Despite the fact that greener techniques have numerous advantages they also have undesirable features. For instance, with usage of ionic liquids there is no need to worry about the emission of VOC. However, ionic liquids do not always enhance the selectivity of the catalyst. In addition, they are not cheap and often toxic, they have high viscosity and additional steps are needed to improve purity. Green alternatives in synthesising organic derivatives in solvents to utilize ultrasound or MW irradiation are more energy efficient, although, these mean similar reactions in comparison to conventional techniques such as reflux treatment. HSBM is a unique method in green chemistry. Indeed, it

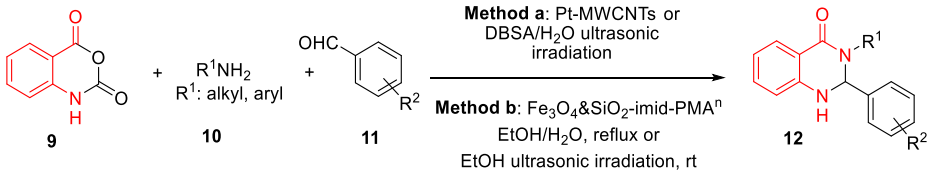
is really an energy effective method. Under HSBM conditions the amount of solvent can be reduced and even solventless reactions can be carried out. This great method is capable of increasing selectivity of asymmetric reactions and it can significantly shorten reactions. The probable reason behind this could be the lack of solvation effects and it is favourable enough for non-covalent interactions [43,61,62]. There are some factors, which could influence the success of reactions utilizing HSBM. These include the material and size of vessels, the number of balls, frequency applied (Hz), inner temperature (milling with or without thermostat), reaction time and added pauses [43, 63].

There can be found some more environmentally benign approaches to the synthesis of oxindole and 2,3-dihydroquinazoline-4-one derivatives in the literature. For instance, Pal et al. used Amberlyst 15 as catalyst and derived the spiro 2,3-dihydroquinazolin-4(1*H*)-one (**3e**) product after a few minutes of ultrasonic irradiation at room temperature. Moreover, the reaction was not sensitive to air or atmospheric moisture (Scheme 11) [28].



Scheme 11

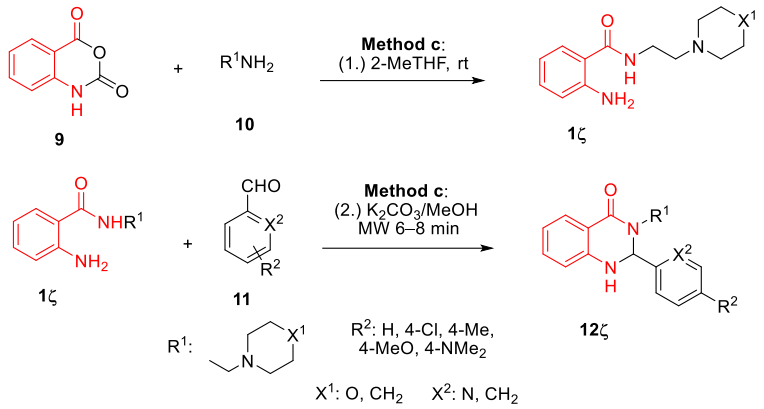
Chen et al. investigated the reaction of **9**, **10** and **11** catalysed by DBSA in aqueous media, under ultrasound irradiation to get 2,3-dihydroquinazolin-4(1*H*)-one compounds **12** (**Method a**, Scheme 12) [64]. Safari et al. examined multi-walled carbon nanotube nanocomposites as catalyst to promote one-pot, three-component coupling reaction of **9**, **10** and **11** under ultrasound irradiation to get 2,3-dihydroquinazolin-4(1*H*)-one compounds **12** (**Method a**, Scheme 12) [65].



Scheme 12

Furthermore, Esmaelipour et al. in 2017 utilised ultrasonic irradiation to synthesise dihydroquinazoline derivatives **12** and obtained better results in yields in comparison to reflux (**Method b**, Scheme 12) [66].

El-Faham et al. developed a new protocol for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-one derivatives **12** (Scheme 13).



Scheme 13

The first step (**Method c** (1.)) consists of the synthesis of 2-amino-*N*-(2-substituted-ethyl)benzamide from isatoic anhydride in which they used 2-MeTHF as an environmentally benign alternative of THF. In the second step (**Method c** (2.)), 2-aminobenzamide intermediate was reacted with numerous aldehydes under MW irradiation, utilising MeOH as solvent and K_2CO_3 as catalyst to afford final product **12ζ** (Scheme 13) [67].

In the synthesis of 2,3-dihydroquinazolin-4(1*H*)-one derivatives **12** and spiroindoline quinazoline derivative **3e**, green techniques were also applied mostly MW and ultrasonic irradiation (Table 5) [28,64–69].

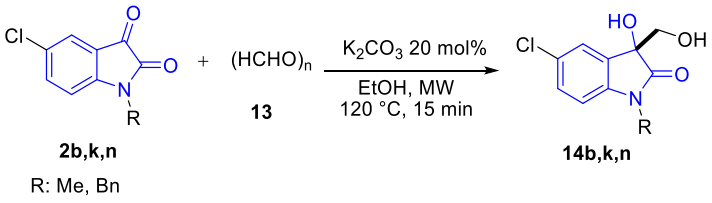
Table 5 Synthesis of 1-(prop-2-ynyl)-1H-spiro[indoline-3,2-quinazoline] 2,4(*3H*)-dione **3e** and 2,3-dihydroquinazolin-4(1*H*)-one derivatives **12** carried out under greener conditions.

Catalyst	Technique	Conditions	Literature
Amberlyst 15	ultrasound	solvent, rt, 1–30 min	Pal et al. 2013[28]
DBSA	ultrasound	40–42 °C, 2–3 h	Li et al. 2015[64]
nanocatalyst	ultrasound	rt, 8–20 min	Safari et al. 2017[65]
nanocatalyst	ultrasound	rt, EtOH, 30 min	Esmaelipour et al. 2016[66]
K_2CO_3/MeOH	MW	6–8 min	El-Faham et al. 2019[67]
$SnCl_2$ 1 mol%	MW	EtOH, 120 °C, 20 min	McCluskey et al. 2020[68]
Amberlyst 15	MW	solvent free, 3 min	Surpur et al. 2007[69]

Pal et al. tested a few minutes of ultrasonic irradiation to obtain 1-(prop-2-ynyl)-1*H*-spiro[indoline-3,2-quinazoline]-2,4(*3H*)-dione (**3e**) to make the synthesis route environmentally benign [28]. Other research groups, such as Li and colleagues, examined the synthesis of 2,3-disubstituted-2,3-dihydroquinazolin-4(1*H*)-one derivatives **12** mainly under

ultrasound irradiation at 40–42 °C. They used DBSA as catalyst in the reaction of **9**, **10** and **11**, affording product **12** in good yields of 80–92% within a few hours in aqueous media [64]. In addition, both Safari et al. (2017) and Esmaelipour and co-workers (2016) also applied ultrasonic irradiation to synthesise dihydroquinazoline derivatives **12** and obtained better results in yields compared to those achieved with conventional methods [65, 66]. On the other hand, El-Faham et al. in 2019, McCluskey et al. in 2020 and Surpur et al. in 2007 investigated the green possibilities of MW irradiation in the synthesis of 2,3-dihydroquinazolin-4(1*H*)-one derivatives **12** [67–69]. McCluskey and colleagues improved an approach to obtain 2,3-dihydroquinazolin-4(1*H*)-ones. They applied a catalytic amount (1%) of $SnCl_2$ to afford the pure material. The process required about a 20-minute MW irradiation at 120 °C. Then the crude product was cooled and subsequent filtration delivered 2,3-dihydroquinazolin-4(1*H*)-ones in good yields of 17–99% [68]. Unfortunately, heating $SnCl_2$ can cause toxic chlorine-containing fumes and it can be especially dangerous by size increases. With the help of MW irradiation reaction times were significantly shortened (1–3 or 20 minutes) [68,69]. Surpur et al. examined the three-component condensation reaction between isatoic anhydride **9**, substituted anilines **10** and benzaldehyde **11** in the presence of MW under neat conditions. They tested several solid Brønsted acid catalysts and Amberlyst 15 was found to be the best choice [69].

Regarding the synthesis of oxindole derivatives, numerous studies were reported performed under milder conditions; for instance, solvent-free synthesis at room temperatures or with low amount of catalyst used. In fact, greener methods or techniques for aldol reaction is a rare thing. Zhang et al. developed a greener way to access 3,3-disubstituted oxindoles via MW-assisted Cannizzaro/aldol reactions of paraformaldehyde (**13**) with isatins **2b**, **2k** and **2n** (Scheme 14) [70].



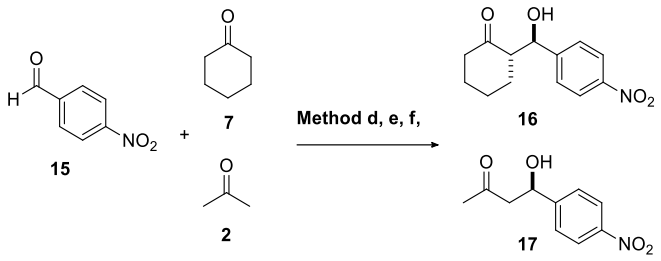
2b,k,n

R: Me, Bn

14b,k,n

Scheme 14

An additional example is by Bolm et al. utilising 10 mol% (*S*)-proline or (*R*)-proline as catalyst in the aldol reaction of 4-nitrobenzaldehyde **15** and cyclohexanone **7** or acetone **2** under ball-milling conditions (4–6 Hz) without solvent. Results in stereoselectivity are better in comparison to conventional methods like magnetic stirring (**Method d)** (Scheme 15) [71].



Scheme 15

Furthermore, Juaristi et al. in 2014 also examined the synthesis of **16** under HSBM circumstances, milling the mixture of **7** and **15** at 15 Hz and 10 mol% (*S*)-proline-containing α,β dipeptides as catalysts for 30 minutes (**Method e**) (Scheme 15) [72]. In addition, Bolm et al. in 2009 also investigated the reaction between **7** and **15** with 20 mol% (*S*)-proline catalyst loading under ball-milling conditions (6 Hz for 15 minutes after 5 minutes pause (**Method f**) (Scheme 15). They obtained product **16** with 58–99 *ee*% after 24 hours [73]. Tanaka et al., in turn, in 2013 investigated the reaction of 4-nitrobenzaldehyde **15** and ketones such as cyclohexanone **7** to get compounds **16** and acetone **2** as well to obtain (*R*)-4-hydroxy-4-(4-nitrophenyl)butan-2-one **17** under HSBM conditions milling at 1.6 Hz for 48 hours [74].

In the case of the aldol reaction of isatin and acetone, only a few research groups utilised greener techniques (for example CF or HSBM) (Table 6) [55,75]. Kinsella and colleagues studied the aldol reaction between isatins **2b**–**d**, **2f**–**i**, **2k**, **2ab**, **2ac**, **2ad** and acetone **5** under CF condition. They applied different solvents with DMF being the best at 40 °C. Reactions were completed after 12-hour residence time forming the (*S*)-aldol products **6b**–**d**, **6f**–**i**, **6k**, **6ab**, **6ac** and **6ad** with excellent *ee* values [55]. Furthermore, Juaristi et al. investigated (*S*,*S*)-thio dipeptides under HSBM conditions at 46 Hz and at –20 °C. Products **6a**, **6b**, **6h**, **6i** and **6k** were obtained after a four-hour milling procedure [75].

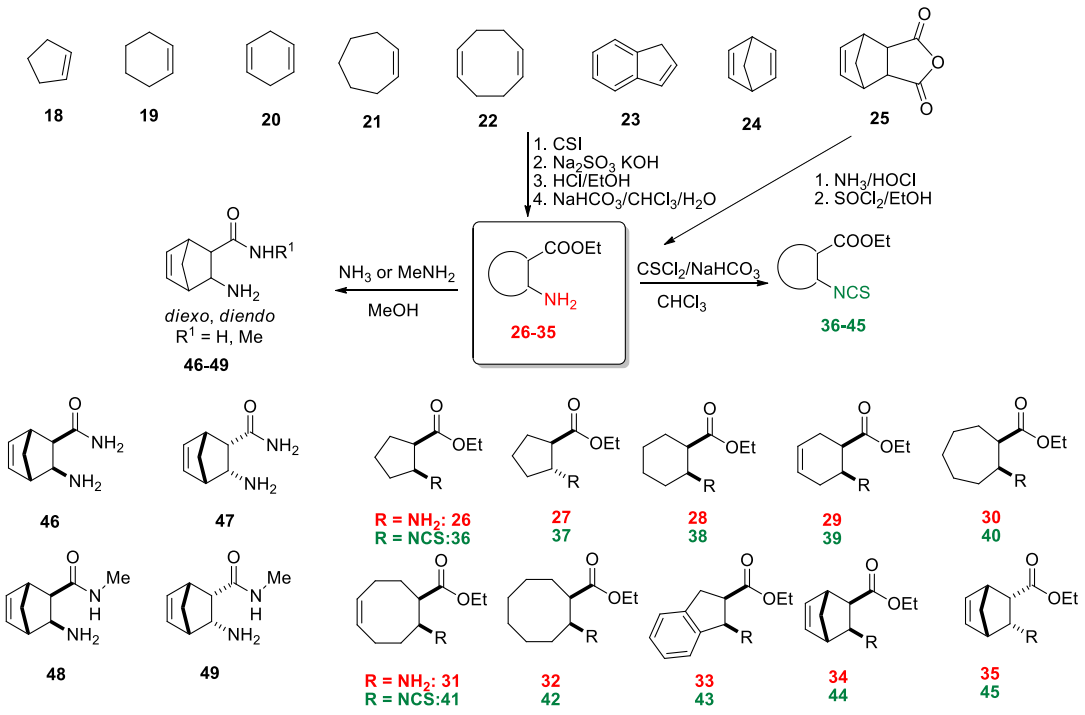
To sum up, there are examples in the literature for greener attempts regarding the synthesis of oxindole-containing aldol products. Some research groups utilised green solvents such as methanol and ethanol, or more environmentally benign catalysts like amino alcohols, amino amides or chiral acid derivatives [2,3,37,38,40,42,43,47–55]. There were efforts to reduce catalyst loadings from 30% to a range between 1–5% [51]. Only a handful of scientists examined the asymmetric aldol reaction of isatin and ketones under HSBM conditions. They achieved better results under HSBM conditions in comparison with conventional techniques [55,75].

3. RESULTS AND DISCUSSION

In order to achieve our goals, the first steps were to synthesise the starting compounds. In the following the synthetic procedures of the desired starting materials and the transformation of these compounds are going to be in focus.

3.1. Synthesis of racemic and enantiomeric starting materials

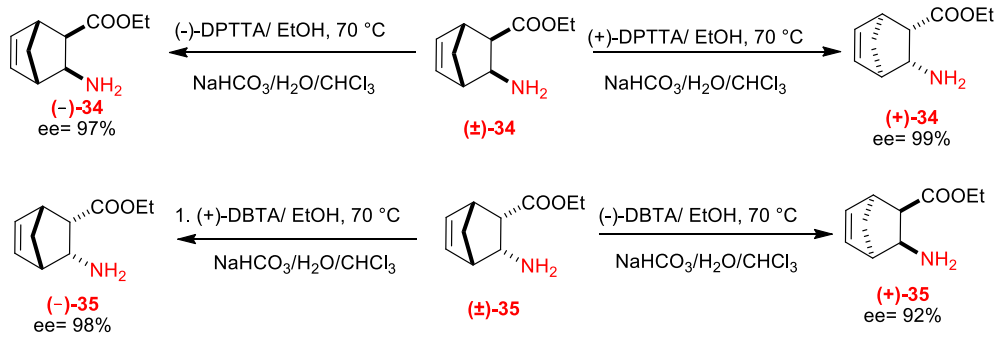
The reaction of chlorosylfonyl isocyanate (CSI) with different cycloalkenes is a well-known route for the synthesis of racemic cycloalkane-fused β-lactams. There are several examples in the literature for the regio- and diastereospecific nature of the cycloaddition, in accordance with the Markovnikov orientation [76], of CSI addition. The synthesis routes were accomplished according to methods already known starting from cyclopentene (**18**), cyclohexene (**19**), 1,4-cyclohexadiene (**20**), cycloheptene (**21**), 1,5-cyclooctadiene (**22**), indene (**23**) and norbornadiene (**24**). [77–89]. Treatment of the β-lactams with ethanolic HCl led to racemic alicyclic amino esters **26**, **28**–**31**, **33** and **34**. Isomerisation of *cis* amino ester **26**, induced by sodium ethoxide, resulted in the formation of *trans* amino ester **27**. In order to get saturated **32**, ethyl *cis*-2-aminocyclooct-5-ene carboxylate **31** was reduced catalytically under H_2. Compound *diendo*-β-amino ester **33** was prepared by hypochlorite-mediated Hofmann degradation of the carboxamide obtained by ammonolysis of anhydride **25**, followed by esterification in the presence of ethanol and then thionyl chloride gave the required product (Scheme 16) [90,91].



Scheme 16

Ethyl 2-isothiocyanato-1-cycloalkanecarboxylates **36**–**45** can be prepared through reaction of esters **26**–**35** with thiophosgene in the presence of $NaHCO_3$ at 40 °C and subsequent column chromatography of the crude oily products. The *diexo*- and *diendo*-2-aminonorbornene esters **34** and **35** were treated with ammonia to furnish the *diexo*- and *diendo*-2aminonorbornene carboxamides **46** and **47** [91,92]. The *diexo*- and *diendo*-*N*-methylcarboxamides **48** and **49** were obtained in the reaction of ethyl ester **34** and **35** with methanolic methylamine (Scheme 16) [93] [I, III].

With the aim of geting enantiopure *diexo*-2-aminonorbornene ester (+)-**34**, we performed the classical diastereomeric salt formation of racemic *diexo*-2-aminonorbornene ester (±)-**34** with (+)-*O*,*O*'-di-*p*-toluoyl-D-tartaric acid ((+)-DPTTA) in EtOH. Furthermore, 2-aminonorbornene ester enantiomer (−)-**35** was prepared through diastereomer salt formation from racemic *diendo*-2-aminonorbornene ester (±)-**35** utilizing (+)-*O*,*O'*-dibenzoyl-D-tartaric acid (DBTA) according to a literature procedure [10]. Racemic *diendo*-2-aminonorbornene ester (±)-**35** was also resolved with (–)-DBTA obtaining enantiomeric amino ester (+)-**35** (Scheme 17) [10] [III].

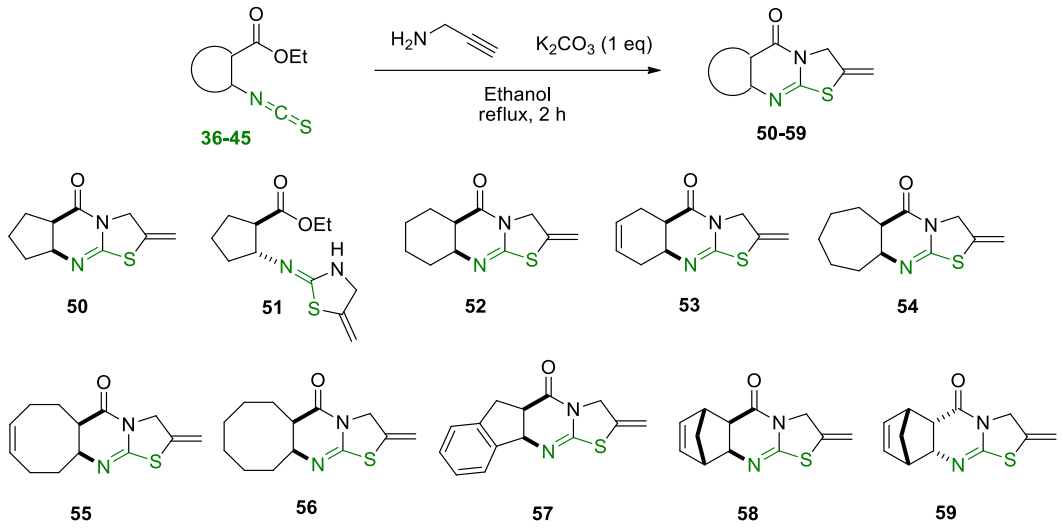


Scheme 17

3.2. Conventional methods for transforming alicyclic β-amino acid derivatives

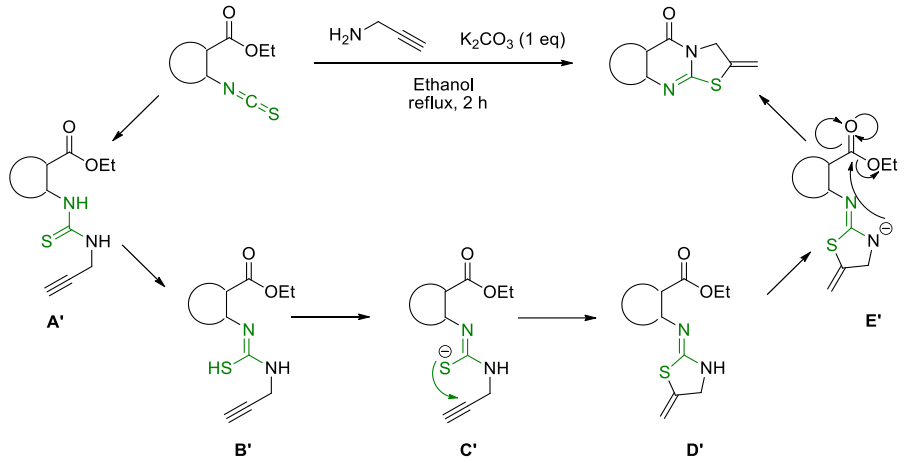
3.2.1. Domino ring closure reaction of alicyclic ethyl 2-isothiocyanato-carboxylates

Synthesis route to fused thiazolo derivatives from alicyclic isothiocyanates bearing an ester group and bifunctional reagents, for instance propargylamine, are advantageous [94–97]. Alicyclic ethyl 2-isothiocyanatocarboxylates **36**–**45** were treated with one equivalent each of propargylamine and potassium carbonate in EtOH under reflux to get products **50**–**59** with relatively high yields, ranging from 68% up to 85% (Scheme 18).



Scheme 18

This reaction process proved to be highly satisfactory, because it showed no decrease of yields when using more flexible alicyclic starting compounds. Partial epimerisation of *cis*-cyclohexane **52** and *cis*-cyclohexene **53** derivatives during the reaction can be avoided by using a weaker base, for example, potassium carbonate. In a possible mechanistic interpretation, product formation involves a two-step cascade reaction starting by the formation of thiourea intermediate A′. The second step is a favoured base-catalysed intramolecular 5-*exo*-*dig* ring closure leading to methylenethiazolidin-2-ylidene intermediate D′. Finally, a base-catalysed amidation delivered the target ring system (Scheme 19). In accordance with a suggested mechanism, first an intramolecular 5-*exo*-*dig* ring closure occurs. This can be confirmed by the following data: regarding the reaction of *trans*-ethyl-2-(3-(prop-2-yn-1-yl) thioureido)cyclopentane-1-carboxylate **27**, accomplished under the same conditions, only methylenethiazolidin-2-ylidene intermediate **51** was obtained as shown by NMR.

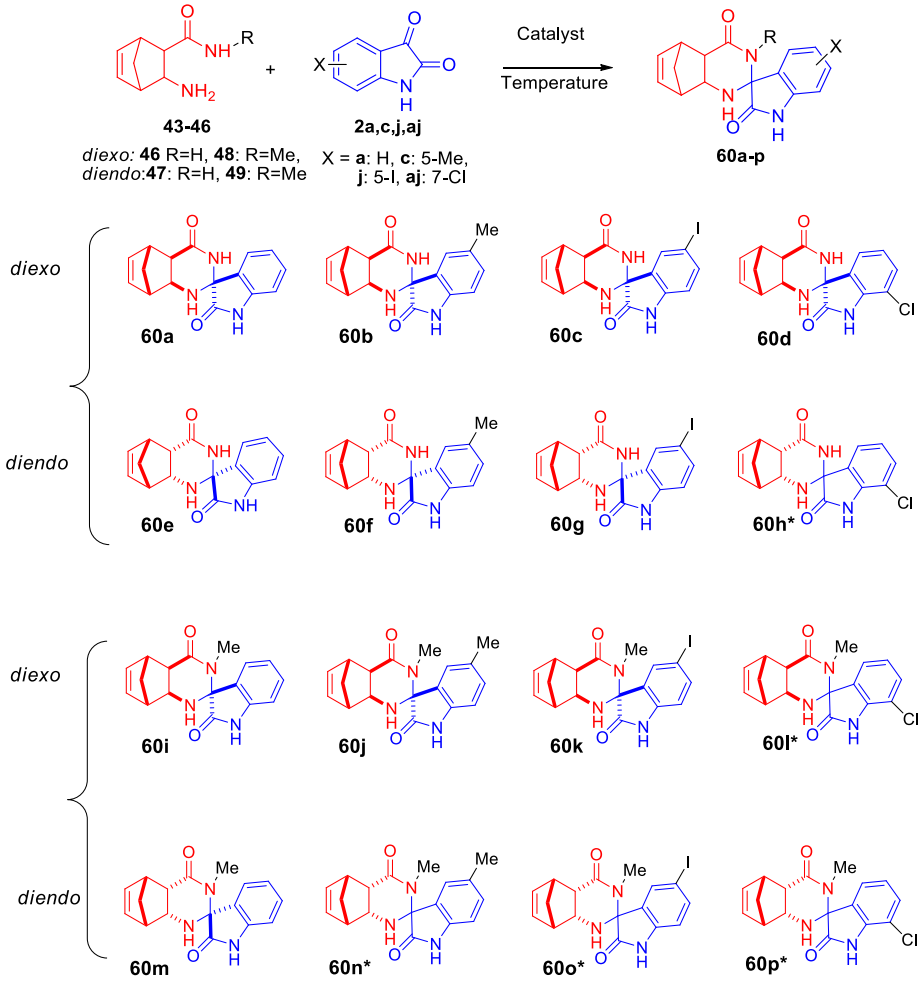


Scheme 19

Additionally, the antiproliferative features of compounds **50**–**59** were investigated determining modest activities. The MCF-7 breast cancer cell line was found to be the most sensitive to almost each of the tested compounds, with a maximum value above 60% growth inhibition presented by compound **57** at a concentration of 30 μM. The indane moiety in the molecular structure seems to contribute to the in vitro anticancer effect [I].

3.2.2. Spiro-condensation reaction of racemic diexo- and diendo-2-aminonorbornene carboxamides

In the synthesis of spiro[5,8-methanoquinazoline-2,3'-indoline]-2',4-dione derivatives **60a**–**p**, spiro-condensation reaction of alicyclic *diexo*- and *diendo*-2-aminonorbornene carboxamides **46**–**49** and isatin derivatives **2a, 2c, 2j, 2aj** were utilised (Scheme 20).



Scheme 20

The influence of several catalysts, solvents and the temperature was studied in the spiro-condensation reaction of isatin **2a** and alicyclic *diexo*-β-amino amide **46** in order to obtain 4a,5,8,8a-tetrahydro-1*H*-spiro[5,8-methanoquinazoline-2,3'-indoline]-2',4(3*H*)-dione (**60a**) to

find the best yield and to develop a simpler reaction route. Catalysts, such as NH_4Cl, $KAl(SO_4)_2 \cdot 12H_2O$ (alum), LiOH, *p*-TsOH, Amberlyst 15 and I_2, were tested with 30 mol% catalyst loading at ambient temperature and under heating in different solvents. Regarding solvents, green ones like ethanol, glycerol, 2M2B and water were tested (Table 6).

Table 6 Synthesis of 4a,5,8,8a-tetrahydro-1*H*-spiro[5,8-methanoquinazoline-2,3'-indoline]-2',4(3*H*)-dione (**60a**).[a]

Entry	Catalyst	Solvent	Temp. (°C)	Time (h)	Yield[a] (%)
1	NH_4Cl	EtOH	rt	24	29[b]
2	NH_4Cl	EtOH	78	12	37[b]
3	NH_4Cl	2M2B[c]	100	9	**35**
4	LiOH	EtOH	rt	72	10
5	LiOH	EtOH	78	72	21
6	*p*-TsOH	EtOH	rt	168	–
7	*p*-TsOH	EtOH	78	168	–
8	Amberlyst 15	EtOH	rt	120	20[b]
9	Amberlyst 15	EtOH	78	10	25[b]
10	I_2	EtOH	rt	215	–
11	I_2	EtOH	78	14	**35**
12	Alum	Glycerol	rt	168	–
13	Alum	Glycerol	100	5	–
14	Alum	2M2B[c]	rt	72	–
15	Alum	2M2B[c]	100	168	–
16	Alum	EtOH	78	5	**42**
17	Alum	water	rt	168	–[d]
18	Alum	water	100	8	–[d]

[a]Isolated yield after purification by flash chromatography. [b]The reaction was not selective. According to ^{1}H-NMR spectra, the product contained the mixture of two diastereomers. [c]2M2B: 2-methylbutan-2-ol. [d]The starting materials did not dissolve in water, there was no transformation.

Screening several catalysts, solvents and temperatures in the reaction between **46** and **2a** showed that the most effective ones were NH_4Cl in 2M2B at 100 °C (after 9 hours), iodine (14 hours) and alum in EtOH at 78 °C (within 5 hours), which afforded the best product selectively (Table 6, entries 3,13,18). Heating was necessary, otherwise the reaction was not completed within a long period of time. Somewhat shorter reaction times were little satisfactory with the

application of alum in comparison to iodine. The relative configuration of the newly built stereocenter of **60a** and **60e** was determined by 2D NMR spectroscopy. For **60a**, medium-intensity NOE interactions were detected between the H4′ proton (7.29 ppm) and the H1 amine (3.54 ppm) and between H4′ and the H3 amide (8.35 ppm). In addition, no NOE signals were observed between the indoline protons (aromatic signals) and H4a or H8a, indicating that the six-membered ring of indoline is located far away (> 5 Å) from these hydrogens and the pyrrolidone ring is positioned in the proximity of H4a and H8a (Figure 8).

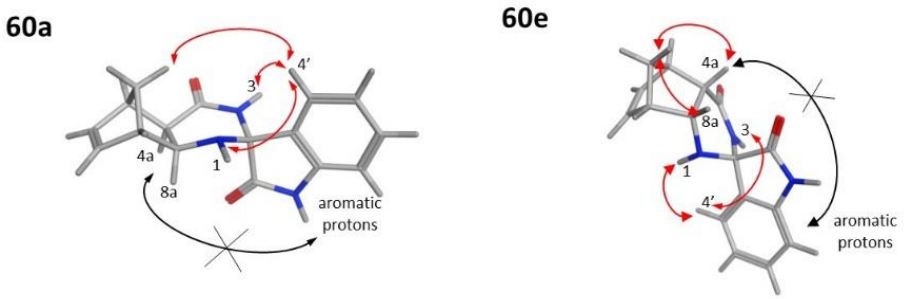


Figure 8

A weak NOESY cross-peak between H4′ and one of the methylene protons (1.82 ppm) provided further support that the aromatic hydrogens are closer to the methylene bridge. In line with the *diexo* configuration, NOEs were not detected between the methylene bridge and the H4a and H8a protons of the norbornene ring. For **60e**, strong NOEs between one of the methylene-bridge protons (1.41 ppm) and H4a (2.81 ppm) and H8a (4.05 ppm), respectively, supported the *diendo* arrangement. The absence of NOE cross-peaks between the aromatic protons of the indoline ring and the H4a and H8a protons indicated that they are not in proximity. Furthermore, NOESY cross-peaks between the methylene and the aromatic hydrogens were not observable, justifying the relative configuration shown in Figure 8. Medium-intensity H4′–H1 (7.14 ppm and 2.38 ppm) and H4′–H3 (7.14 ppm and 8.18 ppm) NOE contacts were also detected. Red arrows show the detected NOESY cross-peaks; black crossed arrows represent missing NOE contacts.

Because the fastest reactions gave the highest yields in EtOH, subsequent syntheses were carried out in this solvent. In order to obtain novel spiro[5,8-methanoquinazoline-2,3'-indoline]-2',4-dione derivatives **60a**–**p**, the syntheses were performed under optimised reaction conditions through conventional method, starting from carboxamides **46**–**49** and unsubstituted **2a**, 5-methyl-substituted **2c**, 5-iodo-substituted **2j** and 7-chloro-substituted isatins **2aj**. In most cases, the reaction of *diexo*-β-amino amide **46** and **48** with isatins **2a**, **2c**, **2j** and **2aj** was selective and it resulted only in a single diastereomer of spiro-quinazolinone derivatives

60a–**d** and **60i**–**k** in low to moderate yields. In a single case of 7-chloroisatin **60d**, the minor diastereomer of **60h** was also formed. The reaction of *diendo*-β-amino amides **47** and **49** with isatin derivatives **2a**, **2c**, **2j** and **2aj** was less diastereoselective, resulting in a single diastereomer of spiro-quinazolinone derivatives **60e**–**g**, **60m** and a mixture in varied ratios of the two diastereomers of spiro derivatives **60n**–**p**. (Scheme 20, Table 7).

Table 7 Synthesis of spiro[5,8-methanoquinazoline-2,3'-indoline]-2',4-dione derivatives **60a**–**p**.[a]

Entry	Amide	Isatin	Time (h)	Product	Yield[b] (%)	de[c] (major:minor)
1	**46**	**2a**	6	**60a**	42	1:0
2	**46**	**2c**	5	**60b**	46	1:0
3	**46**	**2j**	6	**60c**	29	1:0
4	**46**	**2aj**	6	**60d**	30	1:0
5	**47**	**2a**	12	**60e**[d]	35	1:0
6	**47**	**2c**	10	**60f**	37	1:0
7	**47**	**2j**	24	**60g**[d]	30	1:0
8	**47**	**2aj**	24	**60h***[d]	28	1:0.3
9	**48**	**2a**	5	**60i**	46	1:0
10	**48**	**2c**	5	**60j**	42	1:0
11	**48**	**2j**	6	**60k**	24	1:0
12	**48**	**2aj**	6	**60l***	38	1:0.4
13	**49**	**2a**	14	**60m**	31	1:0
14	**49**	**2c**	20	**60n***	24	1:0.4
15	**49**	**2j**	24	**60o***[e]	25	1:1
16	**49**	**2aj**	24	**60p***[e]	34	1.3:1

[a]A mixture of the corresponding isatin (0.13 mmol), β-amino amide (0.13 mmol), alum (20mg, 30 mol%) and EtOH (5 mL) was stirred under reflux for the specified time. [b]Isolated yield after purification by flash chromatography. [c]The diastereoselectivity (major:minor ratio) was calculated by NMR measurements. *mixtures of diastereomers. [d]A mixture of the corresponding isatin (0.13 mmol), β-amino amide (0.13 mmol), I_2 (19 mg, 30 mol%) and EtOH (5 mL) was stirred under reflux for the specified time. [e]A mixture of corresponding isatin (0.13 mmol), β-amino amide (0.13 mmol), NH_4Cl (5mg, 30 mol%) and 2M2B (5 mL) was stirred under reflux for the specified time.

In these days demanding global health problems associated with coronavirus disease 2019 (COVID-19) still require development [98]. Another challenging task for drug design and improvement of the inhibitors of tryptase that has persuasive healing features for treating allergic or inflammatory disorders, such as asthma and inflammatory bowel disease [99]. Moreover, quinazolinone and spiro-quinazolinone derivatives have a wide range of biological

activities, for example, anti-inflammatory, anticonvulsant, antiallergic, antibacterial, antihistamine, antituberculosis and respiratory features [100–102]. The literature background provides examples, where inhibitory characteristics of quinazolinone derivatives were investigated through docking studies [28,100,101,103–105]. For that reason, we decided to examine the following macromolecules for inhibitory applicability of spiro-quinazolinones: (1) a main protease (Mpro) of SARS-CoV-2, which is a crucial enzyme of coronaviruses and it has an essential role in viral replication and transcription (6LU7) [98]; and (2) a protease tryptase, which has an important part in mediating mast cell-dependent allergic and inflammatory responses and making it an attractive drug objective (2ZA5) [99]. Docking studies of a spiro[5,8-methanoquinazoline-2,3'-indoline]-2',4-dione derivatives were carried out *in silico* using SARS-CoV-2 main protease (PDB:6LU7) and human mast cell tryptase (PDB:2ZA5). The predominant aim of this examination was to investigate the inhibitory applicability of spiro[5,8-methanoquinazoline-2,3'-indoline]-2',4-dione derivatives on two, diverse and compelling macromolecules and to compare the results. The results of the present study could deliver a broad knowledge about the inhibitory mechanism of spiro-quinazolinone compounds on tryptase and protease and they support the development of novel derivatives with biological activity.

Compounds **60b**, **60d** and **60f** were found to be promising amongst our sixteen novel compounds, according to our calculations regarding the estimated total energy (complexes of spiro-quinazolinone derivatives and macromolecules) and binding affinity values. In particular, derivative **60d** turned out to be outstanding in inhibitory applicability. Ligand interactions were visualised and analysed through PyMOL 2.5 (The PyMOL Molecular Graphics System, Version 2.5 Schrödinger, LLC) and Discovery Studio Visualizer (BIOVIA, Dassault Systèmes, BIOVIA Discovery Studio, 4.5, San Diego: Dassault Systèmes, 2021). Visualising the results could provide a better understanding regarding the orientation of ligands and bindings with residues (Figure 9 and 10).

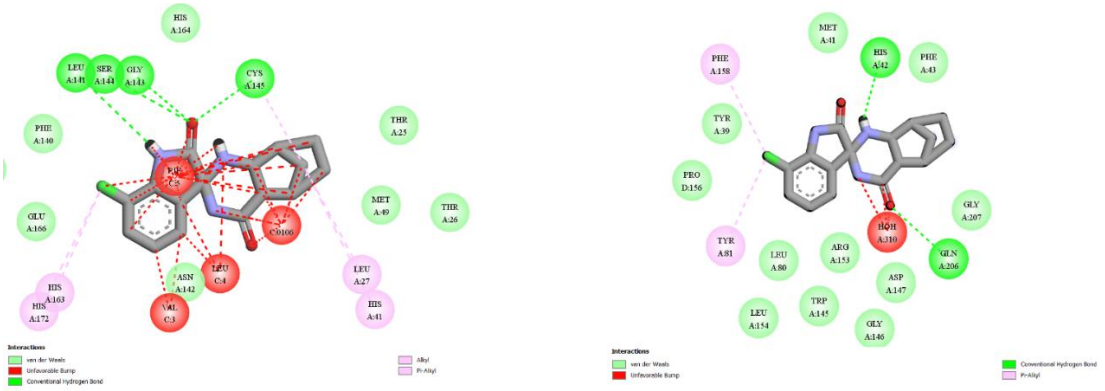


Figure 9: Left:2D interaction map between PDB: 6LU7 and **60d**. Right: 2D interaction map between PDB: 2ZA5 and **60d**.

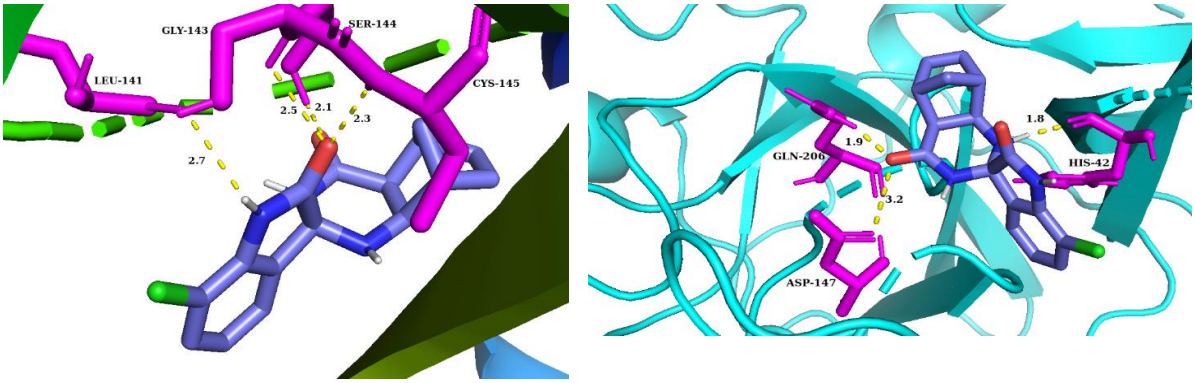
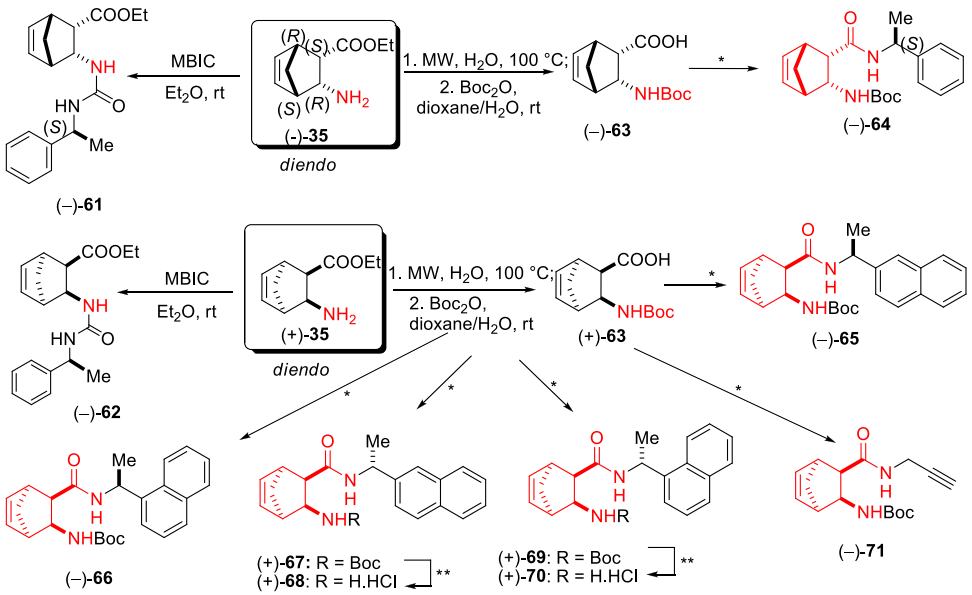


Figure 10 Left: Molecular interactions and binding pose of compound **60d** at the interface of SARS-CoV-2 main protease (PDB: 6LU7), H bonds between the macromolecule and compound **60d** are shown as yellow dashes and distances are in Å units; Right: Molecular interactions and binding pose of compound **60d** at the interface of human tryptase with potent non-peptide inhibitor (PDB: 2ZA5), H bonds between the macromolecule and compound **60d** are shown as yellow dashes and distances are in Å units.

We propose that the chlorine atom of **60d** has high electronegativity property and it can form H-bonds and electrostatic interaction as well with amino acid residues at both hydrophobic and hydrophilic environments. These features are truly advantageous for inhibitory tasks. The results of docking studies could give an understanding of the inhibitory mechanism of spiroquinazolinone derivatives on tryptase and the SARS-CoV-2 main protease, and they may assist in developing novel compounds with biological activities. Moreover, the pharmacokinetic properties of our new compounds **60a**–**p** were predicted with the use of SwissADME web tool. Summarizing the ADMET data predictions by the SwissADME web tool theoretically predicted that our novel tetrahydro-1*H*-spiro[5,8-methanoquinazoline-2,3′-indoline]-2′,4-dione derivatives could be promising biologically active molecules. Moreover, they could be orally active, and they could penetrate the skin according to theoretical predictions by SwissADME.

3.2.3. Transformations of diexo- and diendo-2-aminonorbornene ester enantiomers

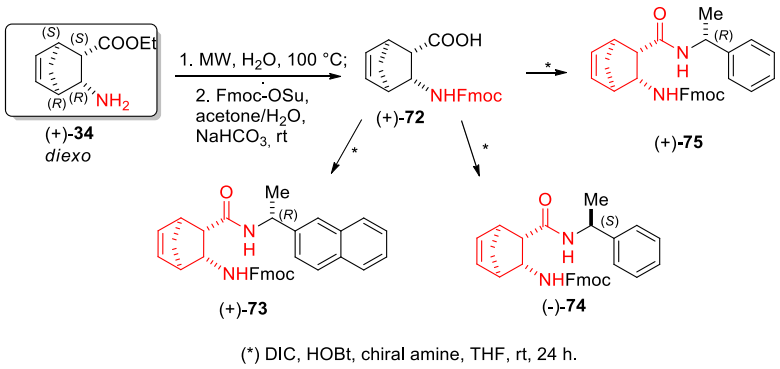
Starting from *diexo*- and *diendo*-2-aminonorbornene ester enantiomers, urea and amide-type chiral derivatives were synthesised. Urea compounds (–)-**61** and (–)-**62** were produced in a good yield, in the reaction of free ester enantiomers (−)-**35** or (+)-**35** and (*S*)-(–)-α-methylbenzyl isocyanate in Et_2O at ambient temperature. The hydrolysis of enantiomer *diendo* free ester (−)-**35** afforded the corresponding amino acid, which was then reacted with Boc_2O in dioxane/H_2O at room temperature to produce enantiopure *diendo* norbornene *N*-Boc-protected amino acid (−)-**63** [106]. The opposite enantiomer of protected amino acid (+)-**63** was synthesised in a similar way. Boc-protected amino acids were converted in acid–amine coupling reactions with different kinds of amines in THF at room temperature in the presence of DIC and HOBt, resulting in amide derivatives **64**–**71** (Scheme 21) [III].



(*) DIC, HOBt, corresponding amine, THF, rt, 24 h. (**) HCl/EtOH, 100 °C, 1 h

Scheme 21

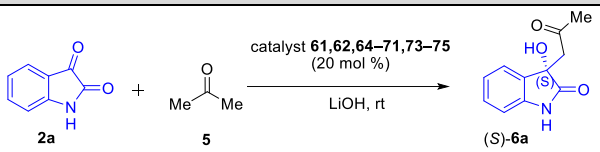
Enantiomeric *diexo* ester base (+)-**34** was hydrolysed into amino acid in a MW reactor. After that it was protected with Fmoc-OSu to yield *diexo*-*N*-Fmoc-protected norbornene β-amino acid (+)-**72** [14]. Starting from (+)-**72**, the following derivatives were prepared via acid–amine coupling processes: (+)-**73** using (*R*)-(+)-1-(2-naphthyl)-ethylamine, (−)-**74** utilizing (*S*)-(–)-1-phenylethylamine and (+)-**75** applying (*R*)-(+)-1-phenylethylamine (Scheme 22) [III].



Scheme 22

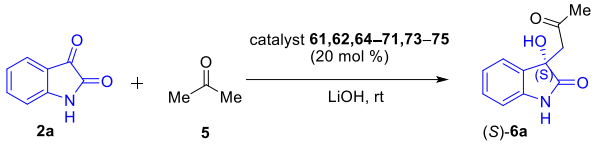
In accordance with our goals to examine greener synthesis procedures and organocatalytic applicability of the alicyclic β-amino acid derivatives and to study the organocatalytic usage of substituted enantiomeric alicyclic β-amino amides in asymmetric aldol reaction of isatin and acetone, we tested our novel compounds **61**, **62**, **64**–**71**, **73**–**75** in asymmetric aldol reaction. In the beginning, catalysts **61**, **62**, **64**–**71**, **73**–**75** were screened at a 20 mol% concentration at room temperature. A very small amount (1 mmol) of LiOH as co-catalyst was also used (**Table 8**) [III].

Table 8 Screening of organocatalysts **61**, **62**, **64**–**71**, **73**–**76** in the aldol reaction between isatin **2a** and acetone **5** in the presence of LiOH additive.[a]



Entry	Catalyst	Time (h)	Yield[c]	*ee* (%)[d] (*S*) config.[e]
1	(−)-**61**	2	95	15
2	(−)-**62**	5	90	5
3	(−)-**64**	0.5	94	43
4	(−)-**65**	4	89	Racemic
5	(−)-**66**	3	88	Racemic
6	(+)-**67**	2	90	48
7	(+)-**68**	2	92	51
8	(+)-**69**	3	90	7
9	(+)-**70**	2	96	49
10	(−)-**71**	1	94	3

Table 8 Screening of organocatalysts **61**, **62**, **64**–**71**, **73**–**76** in the aldol reaction between isatin **2a** and acetone **5** in the presence of LiOH additive.[a]



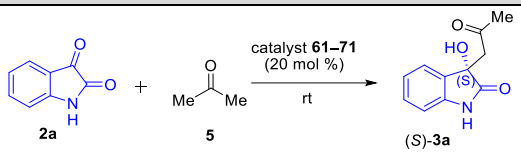
Entry	Catalyst	Time (h)	Yield[c]	*ee* (%)[d] (*S*) config.[e]
11	(+)-**73**	3	89	23
12	(−)-**74**	2	80	3
13	(+)-**75**	3	85	23
14	(−)-**76**[b]	6	96	53

[a]Organocatalysts **61**–**75** (20 mol%), isatin (0.28 mmol), acetone (5 mL, 325 equiv), LiOH (1 mmol) as additive, stirred at room temperature for specified time. [b]Li salt of (*S*)-phenylalanine ((−)-**76**) [42], same amounts of reagents as in case catalysts **61**−**75**, but without additive LiOH. [c]Isolated yield after purification by column chromatography. [d]The *ee* was determined by HPLC using Chiralpak IA column. [e]The absolute configuration was determined by comparison of the specific optical rotation with literature data [2,40, 48,49].

Derivatives (−)-**61**, (−)-**62**, (+)-**67**, (+)-**68** and (+)-**70** afforded quite great results (Table 8, entries 2, 3, 6, 7 and 9). In each case, high conversion value was observed, demonstrated already by TLC monitoring. Contrasting the results considering the *ee* values, enantiomeric excess of (+)-**67** and (+)-**70** represented that the use of β-amino acid derivative (+)-**67**, bearing the *diendo*-norbornene skeleton substituted with the (*R*)-1-(naphthalen-2-yl) ethyl)carbamoyl moiety as catalyst, gave an exceptionally better result, than compound (+)-**69** substituted with the (*R*)-1-(naphthalen-1-yl)ethyl)carbamoyl group (Table 8, entry 6, 8 and 9). One convincing interpretation is that when the catalysts have protecting groups, the transition state of the aldol reaction between isatin and acetone promotes substituent (*R*)-(+)-1-(2-naphthyl) ethyl rather than substituent of (*R*)-(+)-1-(1-naphthyl) ethyl. Although, when the protective groups from (+)-**67** and (+)-**69** were eliminated, (+)-**68** and (+)-**70** produced HCl salts, that worked better than their protected analogue counterparts (Table 9, entries 6 and 8 versus entries 7 and 9). It is worth to mention, that when the Fmoc-protected *diexo*-norbornene β-amino amides (+)-**73** and (−)-**74** were utilised instead of Boc-protected *diendo*-norbornene β-amino amides (−)-**64** and (+)-**67**, large drops were registered in enantiomeric excesses (Table 9, compare entries 3 and 6 with entries 11 and 12). Regarding Fmoc as the protecting group, *ee* values in the reaction between isatin and acetone dropped substantially. The Li salt of (*S*)-phenylalanine (**76**) [42] was utilised in the model reaction between isatin and acetone to reproduce the catalytic activity of (−)-**76**, and it was also used for further new investigations, e.g., with substituted isatins. Probably, it is in connection with a structural reason, especially the serious steric demand of

Fmoc in comparison to Boc. Seemingly, this could have an influence on the corresponding transition state. It is intriguing that examining our catalysts without LiOH as co-catalyst, apart from the hydrochloride salts (+)-**68** (derived from (*R*)-(+)-1-(2-naphthyl)ethylamine) and (+)-**70** (derived from (*R*)-(+)-1-(1-naphthyl)ethylamine), we could achieve quite good results (Table 9, entries 7 and 8) [III].

Table 9 Screening of organocatalysts **61–71** in the aldol reaction between isatin and acetone.[a]

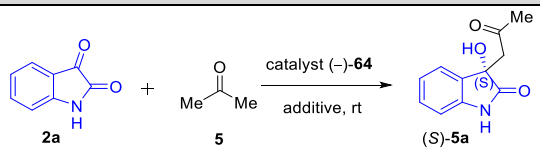


Entry	Catalyst	Time (h)	Yield[b]	*ee* %[c] (*S*) config.[d]
1	(−)-**61**	72	89	7
2	(−)-**62**	90	75	3
3	(−)-**64**	96	70	1
4	(−)-**65**	72	80	Racemic
5	(+)-**67**	72	85	3
6	(+)-**68**	48	90	49
7	(+)-**70**	48	95	57
8	(−)-**71**	48	91	3

[a]Reactions were carried out (20 mol% catalyst loading) with isatin derivatives (0.28 mmol) and acetone (5 mL, 325 equiv); [b]Isolated yield after purification by column chromatography. [c]The *ee* was determined by HPLC using Chiralpak IA column; [d]The absolute configuration was determined by comparison of the specific optical rotation with literature data [2,40,48,49].

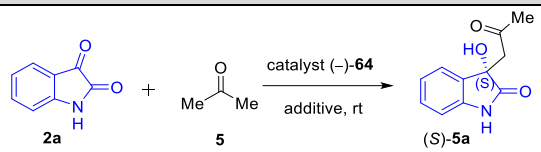
Moreover, when only catalysts without LiOH were applied in the aldol reaction, treatment times had to be expanded significantly. Based on the results shown in **Tables 8** and **9**, derivative (−)-**64**, our best catalyst, was chosen for further analysis. In the following steps the model reaction was optimised to enhance the enantiomeric excess. Thus, the possible effects of additives, catalyst loading, solvent and temperature on the model reaction were tested. At first, different additives were studied in order to increase *ee*% (Table 10) [III].

Table 10 Screening of additives using catalyst **64** in the aldol reaction between isatin **2a** and acetone **5**.[a]



Entry	Additive	Time (h)	Yield (%)[b]	*ee* (%)[c] (*S*) config.[d]
1	TFA	12	75	15

Table 10 Screening of additives using catalyst **64** in the aldol reaction between isatin **2a** and acetone **5**.[a]

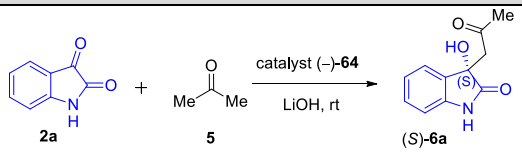


Entry	Additive	Time (h)	Yield (%)[b]	*ee* (%)[c] (*S*) config.[d]
2	HCOOH	12	70	13
3	Benzoic acid	12	80	Racemic
4	H_2O	12	84	3
5	NaOH	4	72	9
6	KOH	4	83	13
7	LiOH	0.5	94	43

[a]Reactions were carried out with (−)-**64** (20 mol%), isatin (0.28 mmol), acetone (5 mL, 325 equiv) and additive (1 mmol) stirred at room temperature for specified time; [b]Isolated yield after purification by column chromatography. [c]The *ee* was determined by HPLC using Chiralpak IA column; [d]The absolute configuration was determined by comparison of the specific optical rotation with literature data [2,40,48,49].

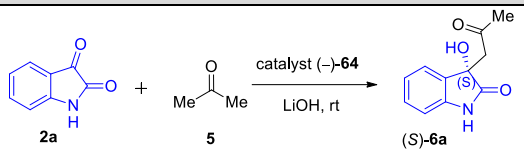
We observed that LiOH applied before is the best additive, since in its presence, the reaction is not only rapid but moderately enantioselective as well (Table 10, entry 7). Other bases also accelerated the reaction, but they failed to provide feasible *ee* values (Table 10, entries 5, 6). When, according to the literature, the most commonly applied additives with acidic characteristic were used in the model reaction instead of LiOH, the reaction became sluggish and hardly enantioselective (Table 10, entries 1–3). The use of water as an additive was also unsuccessful (Table 10, entry 4). Hence, we chose to add a very small amount of LiOH (1 mmol) in further reactions. Afterwards, the influence of various catalyst loadings of (−)-**64** from 5 mol% to 20 mol% were tested on the model reaction (Table 11) [III].

Table 11 Screening of organocatalyst (−)-**64** in varied loadings in the aldol reaction of isatin **2a** and acetone **5** in the presence of LiOH.[a]



Entry	Catalyst mol%	Time (h)	Yield (%)[b]	*ee* (%)[c] (*S*) config.[d]
1	5	30	96	57
2	10	60	89	13
3	15	60	90	11

Table 11 Screening of organocatalyst (−)-**64** in varied loadings in the aldol reaction of isatin **2a** and acetone **5** in the presence of LiOH.[a]

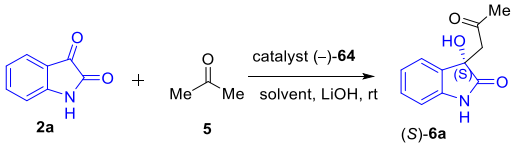


Entry	Catalyst mol%	Time (h)	Yield (%)[b]	*ee* (%)[c] (*S*) config.[d]
4	20	30	94	43

[a]Organocatalyst (−)-**64** in specified mol%, isatin (0.28 mmol) and acetone (5 mL, 325 equiv) stirred at room temperature for specified times in the presence of LiOH (1 mmol); [b]Isolated yield after purification by column chromatography. [c]The *ee* was determined by HPLC using Chiralpak IA column; [d]The absolute configuration was determined by comparison of the specific optical rotation with literature data [2,40,48,49].

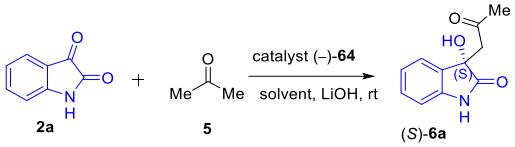
The usage of 5 mol% catalyst under the most environmentally benign conditions provided the greatest *ee* value. Noteworthy, that in this case, a short treatment time was adequate. When the catalyst loading was increased, a sharp reduction in *ee* values and then a rapid surge were observed. Potential background processes, such the retro-aldol reaction, may clarify this phenomenon [59]. In the next steps, the incompletely optimised model reaction (5 mol% (−)-**64** catalyst, 1 mmol LiOH additive, room temperature) was carried out in various bi-component solvents (prepared by mixing 1–163 equivalents of acetone with a polar protic or a polar aprotic solvent) in order to examine the possible solvent effects (Table 12) [III].

Table 12 Screening of different solvents using catalyst (−)-**64** in the aldol reaction between isatin **2a** and acetone **5**.[a]



Entry	Solvent	Acetone equiv	Time (h)	Yield(%)[b]	*ee* (%)[c] (*S*) config.[d]
1	MeOH	163	12	56	39
2	MeOH	65	12	50	7
3	MeOH	6.5	12	67	1
4	MeOH	1	12	48	7
5	EtOH	163	12	73	28
6	EtOH	65	12	75	25
7	EtOH	6.5	12	50	1

Table 12 Screening of different solvents using catalyst (−)-**64** in the aldol reaction between isatin **2a** and acetone **5**.[a]

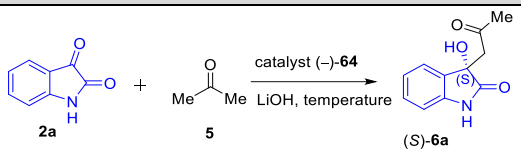


Entry	Solvent	Acetone equiv	Time (h)	Yield(%)[b]	*ee* (%)[c] (*S*) config.[d]
8	EtOH	1	12	69	3
9	2M2B	163	12	60	7
10	2M2B	65	12	70	7
11	2M2B	6.5	12	55	1
12	2M2B	1	12	46	1
13	THF	163	12	78	15
14	THF	65	12	81	1
15	THF	6.5	12	86	5
16	THF	1	12	74	1
17	ACN	163	12	83	3
18	ACN	65	12	86	1
19	ACN	6.5	12	80	9
20	ACN	1	12	89	11

[a]Reactions were carried out with (−)-**64** (5 mol%), isatin (0.28 mmol), acetone (amount given in the table) and solvent (overall volume: 5 mL), in the presence of LiOH (1 mmol), stirred at room temperature for the specified time. [b]Isolated yield after purification by column chromatography. [c]The *ee* was determined by HPLC using Chiralpak IA column; [d]The absolute configuration was determined by comparison of the specific optical rotation with literature data [2,40,48,49].

Concerning the ACN/acetone ratios, the 1:1 mixture produced an almost racemic product, but decreasing the amount of acetone somewhat improved *ee*% **(**Table 12, entries 17–20). In any other cases, the 1:1 mixture brought the highest enantioselectivity, since reducing the amount of acetone largely decreased *ee*% (Table 12, entries 1–16). The aforementioned trend was especially true for acetone/2M2B and acetone/THF mixtures, that is the presence of MeOH and EtOH was well-tolerated. Nevertheless, all the above mixtures resulted in inferior yields and *ee*% values compared to those in pure acetone (Table 11, entry 1). Obviously, acetone was chosen as the solvent in the following tests. Lastly, the possible effect of temperature was studied ranging from –20 °C to 75 °C, under the already optimised conditions (Table 13) [III].

Table 13 Screening of the effect of the temperature on the aldol reaction[a] between isatin **2a** and acetone **5**.[a]



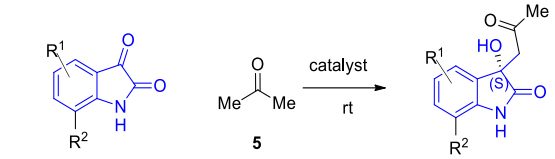
Entry	Temperature	Time (h)	Yield (%)[c]	*ee* (%)[d] (*S*) config.[e]
1	–20	48	89	3
2	4	48	90	1
3	25	0.5	96	57
4	50[b]	0.5	92	Racemic
5	75[b]	0.5	87	Racemic

[a]Isatin (0.28 mmol), organocatalyst (−)-**64** (5 mol%) and LiOH (1 mmol) were dissolved in acetone (5 mL, 325 equiv) and stirred at the specified temperature for the specified time. [b]MW reactor: 50 °C, 75 °C. [c]Isolated yield after purification by column chromatography. [d]The *ee* was determined by HPLC using Chiralpak IA column. [e]The absolute configuration was determined by comparison of the specific optical rotation with literature data [2,40,48,49].

Too high and too low temperatures gave very similar results (Table 13, entries 1, 2, 4 and 5). However, among the tested temperatures, the reaction worked really efficaciously at room temperature (Table 13, entry 3). Performing reactions at room temperature is markedly convenient from a reasonable standpoint [III].

We showed interest about exploring the effect of substrates after adjusting the reaction conditions; hence, numerous substituted isatin derivatives were investigated in model reactions. The goal of this investigation was to determine the issue of substitution of the aromatic ring on isatin. Therefore, 5-methylisatin **2c**, 5-fluoroisatin **2f**, 5-bromoisatin **2h**, 5-nitroisatin **2i**, 5-iodoisatin **2j**, 7-chloroisatin **2aj** and 4,7-dichloroisatin **2ak** were examined. As reported in **Table 14**, catalysts (−)-**62** (entries 3, 6, 9, 12, 15, 19 and 23), (−)-**64** (entries 2, 5, 8, 11, 14, 18 and 22), (+)-**70** (entries 16 and 20) and (−)-**76** (entries 1, 4, 7, 10, 13, 17, 21 and 24) were examined under the already optimised reaction conditions (acetone as solvent, 5–20 mol% catalyst, room temperature, LiOH additive (1 mmol) in the cases of catalysts (–)-**62**, (–)-**64**, no additives in the cases of catalysts (+)-**70** and Li salt of (*S*)-phenylalanine ((–)-**76**) [III].

Table 14 Screening of different isatins **2** in the aldol reaction with acetone **5**.[a]



2a, **2c**, **2f**, **2h-j**, **2aj**, **2ak** **5** (*S*)-**6a**, **6c**, **6f**, **6h-j**, **6aj**, **6ak**

Entry	Catalyst	R^1	R^2	Product	Time (h)	Yield[b]	ee (%)[c] (S) config.[d]
1	**(−)-76**	H	H	**6a**	48	92	53
2	**(−)-64**	5-Me	H	**6c**	72	74	5
3	**(−)-62**	5-Me	H	**6c**	72	69	15
4	**(−)-76**	5-Me	H	**6c**	72	65	39
5	**(−)-64**	5-F	H	**6f**	72	63	30
6	**(−)-62**	5-F	H	**6f**	72	67	47
7	**(−)-76**	5-F	H	**6f**	72	72	37
8	**(−)-64**	5-Br	H	**6h**	72	64	79
9	**(−)-62**	5-Br	H	**6h**	72	68	75
10	**(−)-76**	5-Br	H	**6h**	72	70	49
11	**(−)-64**	5-NO_2	H	**6i**	72	76	45
12	**(−)-62**	5-NO_2	H	**6i**	72	80	9
13	**(−)-76**	5-NO_2	H	**6i**	72	73	41
14	**(−)-64**	5-I	H	**6j**	72	67	27
15	**(−)-62**	5-I	H	**6j**	72	82	35
16	**(+)-70**	5-I	H	**6j**	50	84	45
17	**(−)-76**	5-I	H	**6j**	48	78	65
18	**(−)-64**	H	Cl	**6aj**	72	75	81
19	**(−)-62**	H	Cl	**6aj**	72	90	93
20	**(+)-70**	H	Cl	**6aj**	70	93	39
21	**(−)-76**	H	Cl	**6aj**	48	81	98
22	**(−)-64**	4-Cl	Cl	**6ak**	72	70	99
23	**(−)-62**	4-Cl	Cl	**6ak**	72	77	83
24	**(−)-76**	4-Cl	Cl	**6ak**	72	82	97

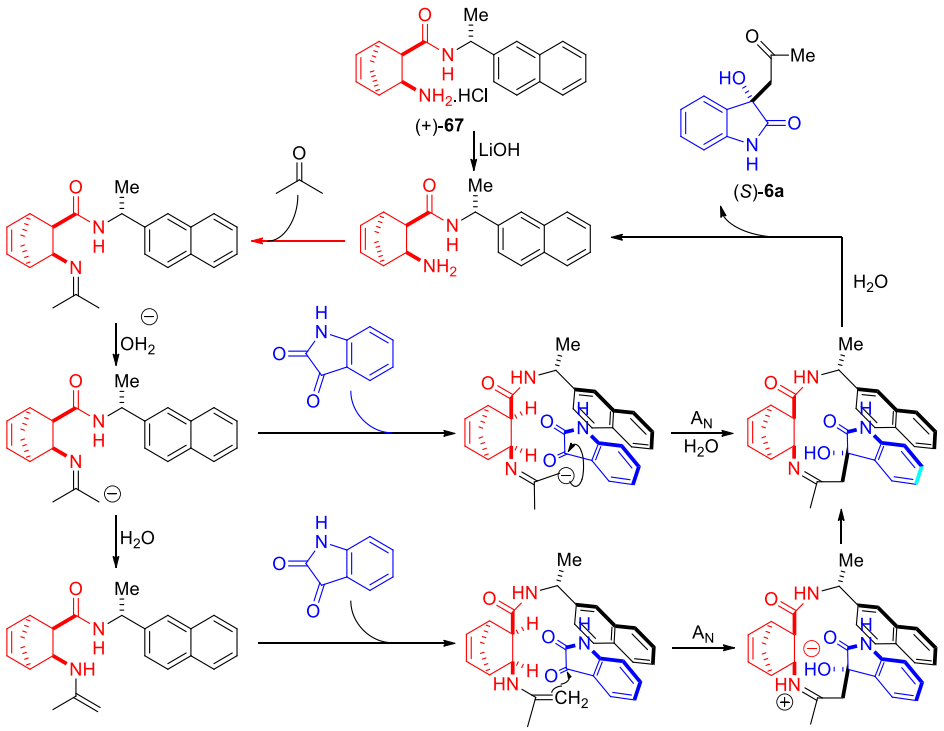
[a]The isatin derivative (0.28 mmol) and the catalyst system [5 mol% (−)-**62** and 1 mmol LiOH; 5 mol% (−)-**64** and 1 mmol LiOH; 20 mol% (+)-**70**; or 20 mol% (−)-**76**] were dissolved in acetone (5 mL, 325 equiv), and stirred at room temperature for the specified time. [b]Isolated yield after purification by column chromatography. [c]The *ee* was determined by HPLC using Chiralpak IA column; [d]The absolute configuration was determined by comparison of the specific optical rotation with literature data [42,49,50,53,55].

First, results with our norbornene catalyst derivatives are discussed. The aldol reaction of 5-methylisatin **2c**, 5-fluoroisatin **2f**, 5-nitroisatin **2i** and acetone **5** yielded moderate results regarding *ee*% (entries 2, 3, 5, 6 and 11, 12). Testing 5-bromoisatin **2h** gave good results (Table 14, entries 8–10), with catalyst (−)-**64** (Table 14, entry 8, 79% enantiomeric excess). Tests with of 5-iodoisatin **2j** and acetone resulted in moderate to good *ee*s (27–45%, Table 14, entries 14–16). When 7-chloroisatin **2aj** and acetone were utilised as substrates, catalyst (−)-**64** afforded the (*S*) product with 81% enantiomeric excess (Table 14, entry 18). Then we examined catalyst (−)-**62**[41] with 7-chloroisatin, which yielded an excellent enantiomeric excess value of 93% of the (*S*) product (Table 14, entry 19). In contrast, 4,7-dichloroisatin **2ak** provided the (*S*) product with excellent enantiomeric excesses of 99% and 83% (Table 14, entries 22 and 23). In general, organocatalysts have been found to give better results in *ee*% values with chlorinated and brominated isatins compared to isatin itself. Guo et al. made similar observations when a chiral diamine catalyst was investigated in the asymmetric cross aldol reaction of isatin **2a** and acetone **5** [54] [III].

Different substituted isatins were also screened with acetone and catalyst (−)-**76** [42] (Table **14**, entries 1, 4, 7, 10, 13, 17, 21 and 24). It is noteworthy that catalyst (−)-**76** [42] was already known in the literature, but it was not investigated with these substituted isatin derivatives. In every context, in particular, when 7-chloroisatin (**2aj**) and 4,7-dichloroisatin (**2ak**) were applied, outstanding enantiomeric excesses were detected (Table **14**, entries 21 and 24, 98% and 97% *ee*s). These results are in agreement with the behaviour of our catalysts (–)-**62** and (–)-**64** derived from β-amino acids as well as the experiences of Guo et al. [54]. In summary, moderately electron-withdrawing chlorine or bromine substituents at the C−4, C−5 and/or C−7 positions of the isatin ring are beneficial to the enantiomeric excess using a wide variety of catalysts [54]. In order to explain our results correctly, it is important to take into consideration that our catalysts, based on their functional groups, can be divided into three definite groups [III].

The first group, β-carbamido esters, has only two models [(–)-**61** and (–)-**62**]. In both cases, the presence of LiOH highly accelerated reactions and partially increased enantioselectivity, but with isatin, *ee* of the product never enhanced above 15% (see Table 8, entries 1 and 2 and Table 9, entries 1 and 2). For that reason, detailed discussion of these catalysts is excluded.

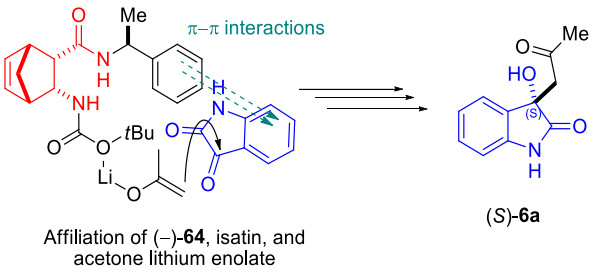
β-Amino amide hydrochloride salts, the representatives of second group, are (+)-**68** and (+)-**70**. Their enantioselectivity is moderate to good (49–57%) and the presence or absence of LiOH had only a minor influence (Table 8, entries 7 and 9 and Table 9, entries 6 and 7). It is interesting, that the side chain chiral centre has also a low effect on their enantioselectivity. Reactions applying these catalysts are hugely accelerated by LiOH. We suggest that these catalysts pursue a mechanism that is very much alike to the one defined by Gavendova et al. [37]. First of all, condensation of acetone with the free amine form of the catalyst affords an imine. After that, LiOH deprotonates this imine to form a somewhat nucleophilic aza-enolate and then nucleophilic enamine is produced by the re-protonation of this aza-enolate. The side chain aryl group of these active species interacts with isatin via π–π stacking, orienting isatin in such a way that Re-face attack of the aza-enolate or enamine is favoured over Si-face attack (Scheme 23) [III].



Scheme 23

This mechanistic interpretation describes that enantioselectivity is an inherent feature of the catalyst (Li^+ is not involved in the orientation of the reagents). The effect of LiOH on the rate of the reaction justifies the theory above. At the beginning, OH^- enhances tautomerisation of imines to enamines. In this the base-promoted tautomerisation aza-enolate intermediates are more nucleophilic and more reactive than enamines. Lastly, LiOH deprotonates the hydrochloride form of the catalyst, converting it into the catalytically active free amine form.

The third group, *N*-Boc-protected β-amino amides, was in the spotlight of our study. As an outcome, this group represents the highest number of compounds (9 derivatives). In this group, the effect of LiOH was examined only in the case of four-membered derivatives. It turned out that LiOH accelerates asymmetric aldol reactions catalysed by (–)-**64**, (–)-**65**, (+)-**67** and (–)-**71**, and it also significantly increases enantioselectivity in the case of catalysts (–)-**64** and (+)-**67** (compare Table 8, entries 3, 4, 6 and 10 with Table 9, entries 3, 4, 5 and 8). Regarding catalyst (–)-**64**, other bases were investigated as well, but they mainly increased reaction rates (see Table 10, entries 4–7). Enamine formation between *N*-Boc-protected β-amino amide compounds and acetone is improbable and the reason behind this is that the nucleophilicity of the Boc-protected nitrogen is reduced substantially. We suggest that these catalysts induce a disparate mechanistic way. First, the reaction between LiOH and acetone produces lithium enolate, which exists as a close ion pair in moderate polarity media. It is a fact that Li^+ owns much stronger coordinative ability than other alkali metal ions (because the small size of Li^+ results in high surface charge density), and Li^+ rather makes interaction with hard Lewis bases (for example oxygen-donor ligands). Therefore, the Li^+ counterion of the enolate can also collaborate with the hard carbonyl oxygen donor atoms of the catalyst. Moreover, the catalyst can also connect with isatin via π–π interactions. As a consequence of these interactions, the Re-face attack is favoured, because isatin and the enolate are oriented in an appropriate way (Scheme 24) [III].



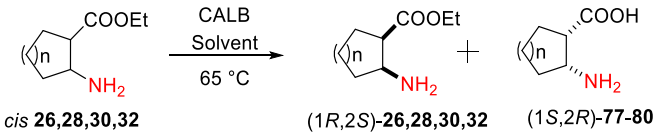
Scheme 24

This mechanism is in accordance with our observations. In the presence of OH^-, the nucleophile would be the enol form of acetone, which is less reactive than the enolate of acetone. Hence, OH^- is accountable for accelerating the aldol reaction. Note that any kind of base with acceptable solubility can accomplish this role (see Table 10, entries 4–7). On the contrary, enantioselectivity specifically needs Li^+, because of its unique and extraordinary coordinative ability, which is essential for orientation of the enolate [III].

3.3. Transformations of alicyclic β-amino acid derivatives: green methods

3.3.1. Transformation of 5–8-membered carbocyclic β-amino esters

In association with our goals to find greener reaction routes for transforming our starting compounds, first we have investigated the optimal conditions for the enantioselective hydrolysis of ethyl *cis*-2-aminocyclopentanecarboxylate (**26**), ethyl *cis*-2-aminocyclohexanecarboxylate (**28**), ethyl *cis*-2-aminocycloheptanecarboxylate (**30**) and ethyl *cis*-2-aminocyclooctanecarboxylate (**32**) (Scheme 25) [II].



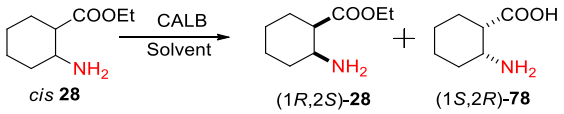
cis **26,28,30,32** (1*R*,2*S*)-**26,28,30,32** (1*S*,2*R*)-**77-80**

n = 1: **26, 77;** n= 2: **28, 78;** n= 3: **30, 79;** n= 4: **32, 80**

Scheme 25

A number of preparatory experiments was accomplished. Apparently, previous results in the CALB-mediated enantioselective hydrolysis of 5- and 6-membered carbocyclic β-amino esters [107], the hydrolysis of the model compound ethyl *cis*-2-aminocyclohexanecarboxylate (**28**) was carried out in iPr_2O without added H_2O. Given that there existed H_2O in the reaction media, the reaction was complete. We attempted to make investigations in different kind of green solvents (Table 15, entries 2–6) [II].

Table 15 Green solvent screening in the hydrolysis of ethyl *cis*-2-aminocyclohexanecarboxylate (**28**)[a] in organic media.



cis **28** (1*R*,2*S*)-**28** (1*S*,2*R*)-**78**

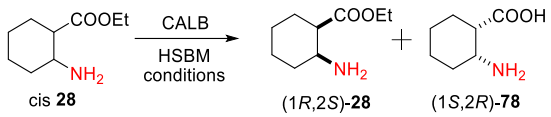
Entry	Solvent (mL)	ee_s (%)[b]	ee_p (%)[c]	Conv. (%)[d]	E[e]
1	iPr_2O	60	95	39	66
2	*t*BuOMe	63	>99	39	133
3	EtOAc	–	–	–	–
4	Propylene carbonate	30	>99	23	73
5	2-Me-THF	14	>99	12	74
6	2M2B	6	>99	6	65

[a]0.025 M substrate, 30 mg mL^{-1} CALB, (substrate: enzyme, 1:7), 1 mL of solvent, at 65 °C after 8 h. [b]According to GC after derivatization. [c]According to GC after double derivatization [108,109].; [d]$c = ee_s/(ee_s + ee_p)$ [110]. [e]$E = \{\ln[(1 - c) \times (1 + ee_p)]/\ln[(1 - c) \times (1 - ee_p)]\}$ [111].

Utilizing *t*BuOMe resulted in better enantioselectivity than usage of iPr_2O reported previously (Table 15, entries 1, 2). In one hand, the results found with propylene carbonate, 2-Me-THF and 2M2B were more moderate regarding conversions and E values (Table 15, entries 4–6). On the other hand, no reaction took place in EtOAc (Table 15, entry 3). For these reasons, we decided to use *t*BuOMe as the best-functioning green solvent for further reactions [II].

In fact, there is an example for the enzymatic hydrolysis of *N*-benzylated-β^3-amino esters applying ball milling [112]. Consequently, **28** was hydrolysed by utilising an HSBM apparatus to examine the enzymatic hydrolysis of ethyl *cis*-2-aminocyclohexanecarboxylate (**28**) (Table 16) [II].

Table 16 Frequency screening in the hydrolysis of ethyl *cis*-2-aminocyclohexanecarboxylate (**28**)[a] throughout milling.



cis **28** (1*R*,2*S*)-**28** (1*S*,2*R*)-**78**

Entry	Frequency (Hz)	ee_s (%)[e]	ee_p (%)[e]	Conv. (%)[f]	E[g]
1	25	2	69	3	6
2	15	3	90	3	19
3	10	5	87	5	16
4	8	5	91	5	21
5	3	15	98	14	147
6[b]	3	16	97	14	89
7[c]	3	24	>99	20	>200
8[d]	3	13	81	14	11

[a]10 mg substrate, 20 mg CALB, (substrate:enzyme 1:2), 0.5 equiv H_2O, 24 µL LAG, agate jars 10 mL, three agate balls with 5 mm diameter, after 6 h using a ball mill. [b]without added H_2O. [c]10 mg substrate, 30 mg CALB (substrate:enzyme 1:3), 0.5 equiv H_2O, 24 µL LAG, at 3 Hz after 6 h a ball mill. [d]10 mg substrate, 10 mg CALB (substrate:enzyme 1:3), 0.5 equiv H_2O, 24 µL LAG, at 3 Hz after 6 h a ball mill. [e]According to GC after double derivatization [108,109]. [f]$c = ee_s/(ee_s + ee_p)$ [110]. [g]$E = \{\ln[(1 - c) \times (1 + ee_p)]/\ln[(1 - c) \times (1 - ee_p)]\}$ [111].

Poor conversion and enantioselectivity values were noticed. Hence, we optimised the applied frequency. It turned out that with decreasing frequencies, enantioselectivities enhanced (Table 16, entries 2–5). A frequency of 3 Hz was found to be the most efficient concerning both conversion and E values. When the reaction was accomplished without H_2O at the already optimised frequency (substrate:enzyme ratio 1:2) and *t*BuOMe in a liquid-assisted grinding (LAG), the catalytic activity of the enzyme was not influenced and enantioselectivity persisted

to be high (Table 16, entry 6). Varying the used amount of enzyme showed that in the case of enhancing from 20 mg to 30 mg both the conversion and enantioselectivity improved remarkably (Table 16 entry 7), while reducing to 10 mg a drop in both conversion and E values was measured (Table 16, entry 6 and 8) [II].

Preparative-scale resolution of **28** was done under the adjusted conditions (Table 17).

Table 17 Preparative-scale resolution of ethyl *cis*-2-aminocyclohexanecarboxylate (**28**)[a] in *t*BuOMe, [b]under solvent-free and [c]ball milling conditions.

Entry	Time (h)	ee_s (%)[d]	ee_p (%)[e]	Conv. (%)[f]	E[g]
1[a]	23	96	>99	50	>200
2[b]	2 (22)	35 (>99)	96 (69)	27 (59)	58 (27)
3[c]	8 (67)	20 (98)	>99 (48)	14 (67)	163 (11)

[a]10 mg substrate, 0.5 equiv H_2O, 24 μL LAG, at 3 Hz after 6 h using ball mills. [b]According to GC after double derivatization. [c]According to GC after double derivatization [98,99].; [d]$c = ee_s/(ee_s + ee_p)$ [110]. [e]$E = \{\ln[(1 - c) \times (1 + ee_p)]/\ln[(1 - c) \times (1 - ee_p)]\}$ [111].

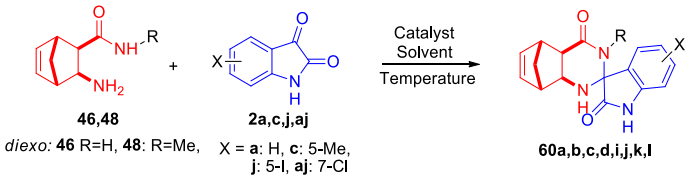
The resolution in *t*BuOMe was accomplished in a single step. Although, trying this at a larger scale, for economic reasons behind, a low (substrate:enzyme 1:4.5) ratio was employed, which afforded excellent enantioselectivity in an acceptable reaction time. Resolutions were done under both solvent-free conditions and using ball milling in two steps. Reactions were stopped at ee_p > 96% (conv. < 50% under-run step) by adding *t*BuOMe to the reaction mixtures and filtering off the enzyme. Next the filtered enzyme was washed with hot distilled H_2O. Amongst preparative-scale resolution of **28**, the most promising condition was the one in *t*BuOMe. Taking these results into consideration, preparative-scale hydrolysis of **26**, **28**, **30** and **32** was accomplished in *t*BuOMe, in the presence of CALB at 65 °C [II].

Effective enzymatic approaches have been improved for the enzymatic resolution of 5–8-membered carbocyclic β-amino esters over hydrolysis in green organic media and using HSBM. Concerning the best E, preparative-scale resolutions were carried out in *t*BuOMe at 65 °C, affording the desired enantiomeric unreacted β-amino esters (1*R*,2*S*)-**26**, -**28**, -**30**, and -**32** and product β-amino acids (1*S*,2*R*)-**77**–**80** with high ee_p values (>96%). The separation of the enantiomers could be accomplished in an easy and favourable way, since the unreacted β-amino esters were soluble in organic solvent and the product β-amino acids in H_2O. According to the best of our knowledge, the lipase-catalysed hydrolysis of seven- and eight-membered carbocyclic β-amino esters was described for the first time in the literature [II].

3.3.2. Environmentally friendly synthesis of spiro[5,8-methanoquinazoline-2,3'-indoline]-2',4-dione derivatives

We put effort in making examinations in CF under HSBM and MW irradiation making the spiro-condensation reaction more environmentally benign and also sustainable. (Table 18).

Table 18 Synthesis of spiro[5,8-methanoquinazoline-2,3'-indoline]-2',4-dione derivatives **60a–d**, **60i–l** under MW irradiation and HSBM conditions.



46,48
diexo: **46** R=H, **48**: R=Me,

2a,c,j,aj
X = **a**: H, **c**: 5-Me, **j**: 5-I, **aj**: 7-Cl

60a,b,c,d,i,j,k,l

Entry	Method	Product	R	X	Time (h)	Yield (%)[d]
1	MW[a]	**60a**	H	H	0.5	85
2	MW[a]	**60b**	H	5-Me	1.5	83
3	MW[a]	**60c**	H	5-I	1	85
4	MW[a]	**60d**	H	7-Cl	2	71
5	MW[a]	**60i**	Me	H	1	70
6	MW[a]	**60j**	Me	5-Me	1.5	65
7	MW[b]	**60k**	Me	5-I	2.5	59
8	MW[a]	**60l***	Me	7-Cl	2.5	60
9	HSBM[b]	**60a**	H	H	6	45
10	HSBM[b]	**60i**	Me	H	6	45
11	HSBM[b]	**60j**	Me	5-Me	6	37
12	HSBM[b]	**60k**	Me	5-I	4	-
13	HSBM[b]	**60l***	Me	7-Cl	4	-
14	CF[c]	**60a**	H	H	0.08[c]	70
15	CF[c]	**60b**	H	5-Me	0.08[c]	62
16	CF[c]	**60d**	H	7-Cl	0.08[c]	70
17	CF[c]	**60n***	Me	5-Me	0.08[c]	52
18	CF[c]	**60p***	Me	7-Cl	0.08[c]	44

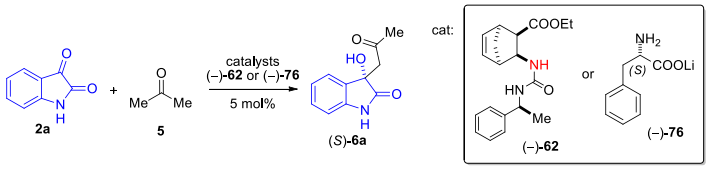
[a]Reaction conditions for MW irradiation: A mixture of corresponding isatin (0.13 mmol), β-amino amide (20 mg, 30 mol%), alum (0.1 mmol) and ethanol (4 mL) were stirred for the specified time at 100 °C. [b]Reaction conditions for HSBM: A mixture of the corresponding isatin (0.13 mmol), β-amino amide (0.13 mmol) and alum (20 mg, 30 mol%), was milled solvent-free for the specified time, using 3 agate balls utilising 15 Hz frequency. [c]Reaction conditions for CF reactions: 0.1 mL min^{-1} flow rate (residence time: 5 min), 100 °C, β-amino amide (c = 0.1 M, 1 equiv.) and isatin (1 equiv.) were dissolved in ethanol (4 mL). *mixtures of diastereomers. [d]Isolated yield after purification by flash chromatography.

Additionally, we studied the synthesis of other products **60b**–**d** and **60i**–**l** under greener conditions (Table 18, entries 2–8, 10–18). The use of the MW reactor turned out to be beneficial to obtain *diexo*-spiro products **60b**–**d** and **60i**–**l** in satisfactory to excellent yields of 60–85% (Table 18, entries 2–8). By this spiro-condensation reaction, where the temperature is a crucial parameter, applying ball milling without thermostat apparatus proved to be less effective in comparison with the MW reactor. Note that under HSBM conditions, **60k** and **60l** could not obtained (Table 18, entries 12,13).

3.3.3. Investigations of the alicyclic β-amino acid derivatives catalysed isatin acetone aldol reaction under greener conditions

In connection with our aims to develop greener asymmetric aldol reaction of isatin and acetone (model reaction), mechanochemical investigations were accomplished. The model reaction was examined under HSBM conditions, testing catalyst loading, milling frequency and reaction time. Each HSBM measurement was done utilising a Retsch 400 Mixer Mill with 10 mL agate jars and 5 mm agate balls. To avoid the rise of the inner temperature of the mill, we used pauses in the milling process. Nevertheless, in the case of using higher frequencies, this approach turned out to be unusable, because of the formation of racemic product. Neither catalyst loading higher than 5 mol% nor using too low and too high frequencies afforded satisfactory results. Applying too low frequency, the reaction time had to be extremely extended. The most successful milling frequencies, which resulted in satisfactory outcomes, were 15 and 20 Hz (Table 19) [III].

Table 19 Screening of the effect of the milling frequency on the aldol reaction[a] in HSBM conditions between isatin **2a** and acetone **5**.

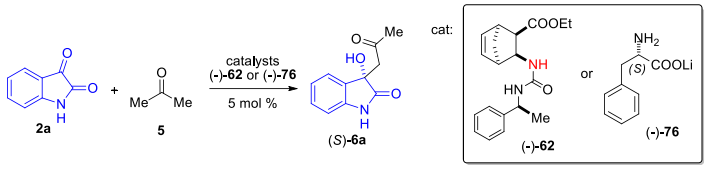


Entry	Catalyst	Frequency (Hz)	Time (min)	Yield (%)[b]	ee (%)[c] (*S*) config.[d]
1	**(−)-62**	15	30	50	ND.
2	**(−)-62**	15	60	56	31
3	**(−)-62**	15	120	48	33
4	**(−)-62**	20	30	61	19
5	**(−)-62**	20	60	59	35
6	**(−)-62**	20	120	43	21
7	**(−)-76**	15	30	67	57
8	**(−)-76**	15	60	65	39
9	**(−)-76**	15	120	61	23
10	**(−)-76**	20	30	70	47
11	**(−)-76**	20	60	69	37
12	**(−)-76**	20	120	61	31

[a]A mixture of isatin (0.28 mmol), LiOH (1 mmol), organocatalyst (5 mol%) and acetone (30 µL, 1.95 equiv) was milled with 3 balls at the specified frequency for the specified time. [b]Isolated yield after purification by column chromatography. [c]The *ee* was determined by HPLC using Chiralpak IA column. [d]The absolute configuration was determined by comparison of the specific optical rotation with literature data [2, 48−50].

It may be estimated that increasing the milling frequency generates an increase of the temperature. This change, however, leads to decreasing enantioselectivity in solution-phase experiments (see Table 19, entries 3–5). The possible effect of the number of milling balls was also investigated. The results displayed that using urea derivative (−)-**62** as catalyst and applying 4 balls gave an excellent result (Table 20, entry 2), while in the case of catalyst (−)-**76**, increasing the number of balls to 4 or 5 provided unsatisfactory results considering *ee*% values (Table 20, entries 5 and 6) [III].

Table 20 Screening of the effect of the number of milling balls at already optimised frequency and catalyst loading on the aldol reaction in HSBM conditions between isatin **2a** and acetone **5**.[a]



Entry	Catalyst	Frequency (Hz)	Number of milling balls	Yield(%)[b]	ee (%)[c] (*S*) config.[d]
1	**(−)-62**	20	3	68	35
2	**(−)-62**	20	4	70	96
3	**(−)-62**	20	5	61	5
4	**(−)-76**	15	3	69	57
5	**(−)-76**	15	4	73	45
6	**(−)-76**	15	5	64	33

[a]A mixture of isatin (0.28 mmol), LiOH (1 mmol), organocatalyst (5 mol%) and acetone (30 µL, 1.95 equiv) was milled with the specified number of balls for the already optimised time. In the case of catalyst (−)-**62**, milling time was 60 min, while regarding catalyst (−)-**76** the milling time was 30 min. [b]Isolated yield after purification by column chromatography. [c]The *ee* was determined by HPLC using Chiralpak IA column. [d]The absolute configuration was determined by comparison of the specific optical rotation with literature data [2, 48−50].

4. Summary

Ethyl *cis*- and *trans*-, *diexo*- and *diendo*-2-isothiocyanato-1-cyclalkanecarboxylates **36**–**45** were prepared by conventional methods, with the reactions of the corresponding alicyclic ethyl 2-amino-1-carboxylates **26**–**35** and thiophosgene. These isothiocyanates underwent a base-promoted cascade reaction with propargyl amine, resulting in 2-methylene-substituted thiazolo[2,3-*b*]quinazolinones and alicyclic thiazolo[3,2-*a*]pyrimidinones **50**–**59**. Note that *trans* isomer **37** failed to cyclise, but gave methylenethiazolidin-2-ylidene intermediate **51**. The cascade reaction proceeds by way of a favoured 5-*exo*-*dig* process during the second ring closure, as confirmed by full NMR spectroscopic assignments. The biological activity of compounds **50**–**59** was tested and modest activities were detected mainly against breast cancer cells. (5a*S**,10b*S**)-2-Methylene-2,3,5a,6-tetrahydroindeno[1,2-*d*]-thiazolo[3,2-*a*]pyrimidin-5(10b*H*)-one (**57**) showed an outstanding biological feature, which may certainly be helpful in developing anticancer drugs [I].

Furthermore, cyclopentane, cyclohexane, cycloheptane and cyclooctane skeletons bearing β-amino esters **26**, **28**, **30** and **32** were successfully synthesised according to literature procedures. These compounds were starting materials in enzymatic hydrolysis with the use of CALB enzyme to obtain unreacted (1*R*,2*S*)-**26**, **-28**, **-30** and **-32** β-amino ester enantiomers and enantiomeric β-amino acids (1*S*,2*R*)-**77**–**80** as a part of greener approaches. In addition, these enzymatic reactions were carried out under HSBM conditions to make them more environmentally benign. HSBM proved to be a beneficial method in the case of enzymatic hydrolysis. What is more, green solvents like propylene carbonate, 2-Me-THF, 2M2B and *t*BuOMe were tested in enzymatic hydrolysis. Of these, *t*BuOMe turned out to be the best working solvent in CALB-assisted enzymatic hydrolysis reactions. Preparative-scale reactions were also done under HSBM conditions [II].

Starting from enantiomeric ethyl 3-aminobicyclo[2.2.1]hept-5-ene-2-carboxylates [(–)-**34**, (+)-**34**, (–)-**35** and (+)-**35**], a large number of organocatalyst **61**–**75** were synthesised, characterised and tested in the aldol reaction between isatin and acetone as a model reaction. Our novel compounds can be divided into the following three different groups: β-carbamido esters (–)-**61**, (–)-**62**, β-amino amide hydrochloride salts (+)-**68**, (+)-**70** and *N*-protected β-amino amides (–)-**64**–(+)-**67**, (+)-**69** and (–)-**71**–(+)-**75**. The applicability of these compounds as organocatalysts were examined in the asymmetric aldol reaction as a chosen model reaction. The model reaction was optimised by screening the additives and solvents used, catalyst

loadings and temperatures to enhance the enantioselectivity of the reaction. The optimised conditions were the following: utilising a very small amount of LiOH as additive, acetone as solvent and reagent, 5 mol% catalyst loading and room temperature. These are the safest and most green conditions. Note that we could remarkably shorten the reaction time to 30 minutes and reduced the used amount of catalyst down to 5 mol% in the case of product (*S*)-3-hydroxy-3-(2-oxopropyl)indolin-2-one (**6a**). To enhance the better understanding of possible reaction mechanisms in this field, we proposed to use our different groups of catalysts. In a nutshell, the reaction of LiOH with acetone generates a lithium enolate. In the presence of OH^-, the enolate of acetone is generated, which is rather reactive. Hence, OH^- is needed for accelerating the reaction. On the other hand, enantioselectivity specifically requires Li^+, because its unique coordinative ability is crucial for the orientation of the enolate. Substrate screening was also accomplished in the aldol reaction of isatin and acetone with numerous substituted isatins, using, for example 5-methylisatin (**2c**), 5-fluoroisatin (**2f**), 5-bromoisatin (**2h**), 5-nitroisatin (**2i**), 5-iodoisatin (**2j**), 7-chloroisatin (**2aj**) and 4,7-dichloroisatin (**2ak**). In harmony with literature data applying substituted isatins, in most cases better results could be achieved up to excellent 99% in *ee* compared to isatin **2a** itself. Moreover, we put an effort to make the model reaction more sustainable through performing the aldol reaction in HSBM. Neither too high nor too low frequencies were favourable in the model reaction and the use of 15 or 20 Hz proved to be a good solution. Moderate results were obtained. Note, however, that investigating the possible effect of the used number of balls, presented an astonishingly good result of 96% *ee* under ball milling condition [III].

Moreover, in order to develop useful derivatives with antitumor and antiallergic features, novel spiro-quinazolinone compounds were designed and synthesised in the following way: *diexo*- and *diendo*-esters **34** and **35** were treated with ammonia to furnish *diexo*- and *diendo*-aminobicyclocarboxamides **46** and **47** [91]. Compounds *diexo*- and *diendo*-*N*-methylcarboxamides **48** and **49** were obtained in the reaction of ethyl esters **33** and **35** with methanolic methylamine [93]. Then 2-amino carboxamides **46**–**49** were transformed through condensation reactions with isatins. For instance, isatin (**2a**), 5-methylisatin (**2c**), 5-iodoisatin (**2j**) and 7-chloroisatin (**2aj**) were applied to obtain novel spiro-quinazolinone derivatives **60a**–**p**. Catalysts, solvents and temperatures were screened in order to optimize the reaction. In accordance with our goals, investigations were done under CF, MW and HSBM conditions in order to make the condensation reaction of β-amino amides and isatins more environmentally benign. Utilising MW irradiation afforded the products with excellent results in yields up to

85%. Moreover, with HSBM usage it had become possible to reduce the amount of used solvent and the product was reached in good yields. *In silico* docking studies were done with spiro[5,8-methanoquinazoline-2,3'-indoline]-2',4-dione derivatives **60a**–**p** in order to facilitate the design of potential biologically useful molecules and promote drug developing. Our innovative compounds showed to be good ligands fitting to SARS-CoV-2 main protease (PDB: 6LU7) and human mast cell tryptase (PDB: 2ZA5). The most promising ligand was compound **60d**, affording excellent results in both cases of macromolecules. In addition, an Absorption, Distribution, Metabolism and Toxicity (ADMET) prediction was also made to forecast, whether our novel compounds are capable of producing orally active drugs or they can penetrate the skin. The importance of the docking and ADMET studies regarding the results of the ADMET prediction, spiro[5,8-methanoquinazoline-2,3'-indoline]-2',4-dione derivatives **60a**–**p** theoretically were shown to be feasible for drug development.

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