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Derivatives of Benzoimidazolylbenzoic Acid as the Axially Chiral
Derivatizing Agent and Organocatalyst

Ph.D. Thesis

Mgr. Michal Kriegelstein

Supervisor: Doc. RNDr. Petr Cankař, Ph.D.

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Mgr. Michal Kriegelstein

Abstract

The thesis deals with the synthesis of axially chiral benzimidazoles and their potential applications in the assignment of absolute configuration and organocatalysis. The introduction part is divided into the three chapters. The first chapter provides an introduction into the area of axially chiral compounds with focus on atropisomers, especially those containing C-N bond as the chiral axis. The remaining two chapters introduce the two main projects.

The first, and major, project deals with the design and development of the novel axially chiral derivatizing agent (CDA) for the NMR assignment of absolute configuration of chiral compounds. Although there are multiple methods that allow the configuration assignment, the common availability of NMR instruments makes this method interesting for the general use. Various CDAs have been already reported together with their limitations in the past. In this chapter, the general principles of the method are summarized and the most relevant CDAs are discussed with their limitations.

The second, minor, project deals with the development of a novel organocatalytic system for an asymmetric reduction of prochiral imines. The current methods are presented with a focus on those using HSiCl_3 as a reducing agent due to its high availability and low price.

The results and discussion chapter is divided into two chapters, each dedicated to one of the mentioned projects. Moreover, the results of each project are discussed, including also various dead ends and unsuccessful attempts. A comparison to relevant data from the literature is included as well.

The experimental part includes detailed experimental procedures for the conducted experiments which are not included in the publications that arose from this thesis.

Abstrakt

Tato disertační práce se zabývá syntézou axiálně chirálních benzimidazolů a jejich potenciálními aplikacemi v oblasti chirálních derivatizačních činidel a organokatalýzy. Úvodní část je rozdělena do tří kapitol, které popisují problematiku chirálních sloučenin se zaměřením na atropisomery. Zbývající dvě kapitoly poskytují úvod do problematiky dvou hlavních projektů, kterými se tato práce zabývá.

První (a hlavní) projekt se zabývá vývojem nového chirálního derivatizačního činidla (CDA) pro určení absolutní konfigurace chirálních sloučenin pomocí NMR spektroskopie. Ačkoliv existuje celá řada jiných alternativních metod, vysoká dostupnost NMR spektrometrů v chemických laboratořích je nespornou výhodou této metody. Několik různých CDA bylo v této oblasti již v minulosti popsáno a využito, nicméně jejich využití není bez omezení. V této kapitole jsou popsány obecné principy těchto metod a nejpoužívanější CDA jsou popsána spolu s jejich limitacemi.

Druhý projekt se zabývá vývojem nového ligandu pro organokatalytické redukce prochirálních iminů. V této kapitole jsou popsány aktuální metody pro organokatalytické redukce prochirálních iminů se zaměřením na využití HSiCl_3 jako redukčního činidla, a to zejména z důvodu snadné dostupnosti a nízké ceny tohoto činidla.

Následuje část Výsledky a diskuse, která je rozdělena na dvě podkapitoly pro každý z výše uvedených projektů. V této kapitole jsou prezentovány a diskutovány výsledky každého z projektů, která jsou dále srovnány s literaturou.

Následuje experimentální část, která popisuje jednotlivé experimenty.

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Writing this thesis was much more difficult than I expected and it would not have been possible without the help and support of many people who were directly or indirectly involved in my work.

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Last, but not least, there are some friends I want to mention: Stanko, Mat'o, David, Ivan, Jaro and Paša I really enjoyed our D&D sessions and I am going to miss our game. I would also like to thank various online friends I met on [chemicalforums.org](https://www.chemicalforums.org), [r/ChemPros](https://www.reddit.com/r/ChemPros) and chemistry discord channel. I had a great time discussing chemistry online and your technical experience proved crucial on multiple occasions.

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Organic chemistry is very specific. One spends a lot of time in the lab. Eighty percent of reactions have negative results. Few of us like this self-torture.

František Zálešák

Contents

List of abbreviations	11
1. Aims of this thesis	13
2. State of the art	14
2.1. Axial chirality	14
2.2. Atropisomers	14
2.2.1. Introduction	14
2.2.2. Stability and racemization of atropisomers	16
2.2.3. Synthesis of biaryl atropisomers	20
2.3. Assignment of the absolute configuration by NMR.....	28
2.3.1. Introduction	28
2.3.2. Analysis of chiral secondary alcohols	30
2.3.3. Other arylmethoxyacetic acids	35
2.3.4. Analysis of amines	40
2.3.5. Analysis of polyfunctional compounds	42
2.4. Organocatalytic HSiCl_3 reduction of ketimines	46
3. Discussion and results: Project NMR.....	56
3.1. Synthesis of 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoic acid.....	56
3.1.1. Introduction	56
3.1.2. Chan-Lam approach	57
3.1.3. Cyclization approach.....	57
3.2. Resolution of enantiomers.....	61
3.2.1. Crystallization	61
3.2.2. Conversion to diastereomers	62
3.3. Atroposelective synthesis	66
3.4. Conformational stability of TBBA.....	73
3.5. NMR results	76
3.5.1. Analysis of α -chiral amines and alcohols.....	76
3.5.2. Analysis of β -chiral alcohols and amines	89
3.5.3. Synthesis of deuterated TBBA	107
3.5.4. Conclusion.....	108
4. Results and discussion: Project catalysis.....	110
4.1. Design of the ligand	110
4.2. Synthesis of benzimidazolone based ligand.....	111
4.3. Synthesis of pyridine-based ligand.....	121
4.3.1. <i>N</i> -arylation based synthesis	122
4.3.2. Cyclization approach.....	123

4.3.3. Resolution of pyridine catalyst 128	127
4.3.4. Modifications of the structure of the ligand 128	130
4.3.5. Atroposelective approach towards ligand 128.....	133
4.4. Reduction experiments	134
4.4.1. Nonlinear effect	138
5. Conclusion.....	140
6. Experimental part	141
7. List of author's publications.....	210
8. List of used literature sources.....	211

List of abbreviations

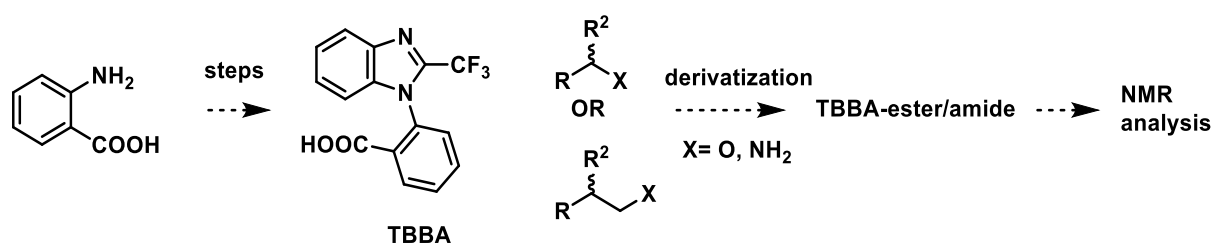
CDA	chiral derivatization agent	Naphth	naphthyl
NMR	nuclear magnetic resonance	Hex	hexyl
Ent	enantiomer	RT	room temperature
BINOL	1,1'-bi-2-naphthol	BINAM	1,1'-bi-2-naphthylamine
HPLC	high performance liquid chromatography	TBBA	2-(2-(trifluoromethyl)-1 <i>H</i> -benzo[<i>d</i>]imidazol-1-yl)benzoic acid
dba	dibenzylidene acetone	TLC	thin layer chromatography
Me	methyl	TMEDA	tetramethylethane-1,2-diamine
TBS	<i>tert</i> -Butyldimethylsilyl	DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
Bn	benzyl	TFA	trifluoroacetic acid
tBu	<i>tert</i> -butyl	MS	mass spectrometry
Ph	phenyl	HPLC-MS	high performance liquid chromatography coupled with mass spectrometry
Tf	trifluoromethylsulfonyl	TFAA	trifluoroacetic acid anhydride
Tol	tolyl, toluene	PE-Mix	
THF	tetrahydrofuran	T3P	2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trioxide
DMF	dimethylformamide	CDI	1,1'-carbonyldiimidazole
NaPhePHOS	(1-(2-(diphenylphosphanyl)-6-methoxyphenyl)naphthalen-2-yl)diphenylphosphane	EDCI	<i>N</i> -Ethyl- <i>N'</i> -(3-dimethylaminopropyl)carbodiimide hydrochloride
BINAL	lithium dihydrido(binaphthoxy)aluminate)	HOBt	1-Hydroxybenzotriazole hydrate
CBS	Corey-Bakshi-Shibata catalyst	TEA	triethylamine
de	diastereomeric excess	pTSA	toluene-4-sulfonic acid monohydrate
ee	enantiomeric excess	SFC	supercritical fluid chromatography
CPA	chiral phosphonic acid	SCDI	1,1'-thiocarbonyldiimidazole
TRIP	(<i>S</i>)-3,3'-Bis(2,4,6-triisopropylphenyl)-1,1'-bi-2-naphthol cyclic monophosphate	10-CSA	10-camphorsulfonic acid
mCPBA	meta-Chloroperbenzoic acid	TBDPS	<i>tert</i> -Butyldiphenylchlorosilane
NHC	<i>N</i> -heterocyclic carbene	ACN	acetonitrile
VCD	vibrational circular dichroism	XPhosPdG2	chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II),
ORD	optical rotary dispersion	TBBACl	2-(2-(trifluoromethyl)-1 <i>H</i> -benzo[<i>d</i>]imidazol-1-yl)benzoyl chloride
CSA	chiral solvating agent	OSU	<i>N</i> -hydroxysuccinimide
MTPA	3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid	MMFF	molecular mechanics force field

MTPA-Cl	3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl chloride	TFAOMe	methyl trifluoroacetate
CIP	Cahn-Ingold-Prelog	DIAD	diisopropylazodicarboxylate
ap	antiperiplanar	HOAc	acetic acid
sp	synperiplanar	DIEA	diisopropylethylamine
MPA	2-methoxy-2-phenylacetic acid	TMSOK	potassium trimethylsilanolate
1-NMA	2-methoxy-2-(naphthalen-1-yl)acetic acid	HATU	1-[bis(dimethylamino)methylene]-1 <i>H</i> -1,2,3-triazolo[4,5- <i>b</i>]pyridinium 3-oxid hexafluorophosphate
2-NMA	2-methoxy-2-(naphthalen-2-yl)acetic acid	Py	pyridine
9-AMAA	2-(anthracen-9-yl)-2-methoxyacetic acid	PPA	polyphosphoric acid
Boc	<i>tert</i> -butoxycarbonyl	Ac₂O	acetic anhydride
Boc-PHG	2-((<i>tert</i> -butoxycarbonyl)amino)-2-phenylacetic acid	LTA mix	Dibenzoyl-L-tartaric acid Dianisoyl-L-tartaric acid Ditoluoyl-L-tartaric acid
DCM	dichloromethane	L-DBT	Dibenzoyl-L-tartaric acid
DMSO	dimethylsulfoxide	L-DTT	Dianisoyl-L-tartaric acid
DMAP	4-dimethylaminopyridine	L-DAT	Ditoluoyl-L-tartaric acid
DCC	dicyclohexylcarbodiimide	TES	triethylsilane
HMPA	hexamethylphosphoramide	NLE	nonlinear effect
Ts	tosyl	(-)-NLE	negative nonlinear effect
Cp	cyclopentyl	(+)-NLE	positive nonlinear effect

1. Aims of this thesis

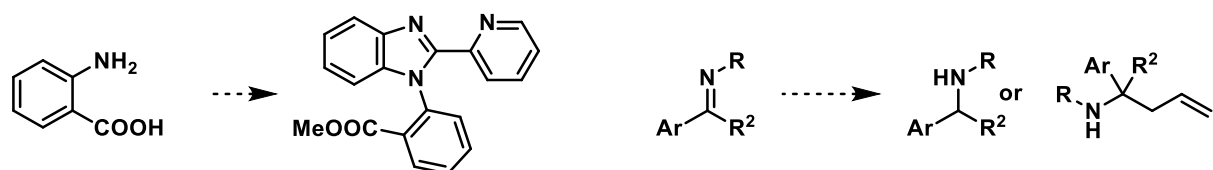
1) Development of novel chiral derivatization agent for NMR spectroscopy

The synthesis and resolution of an axially chiral benzimidazole derivative as a chiral derivatization agent (CDA) and its study of capability to distinguish between the enantiomers of the analyte based on the ^1H , ^{13}C , or ^{19}F NMR spectra. For this application, a conformational model for the assignment of absolute configuration deduced from the NMR data and in-silico modeling of model compounds will be designed.



2) Design and development of an organocatalytic system for the asymmetric additions of organosilicon reagents to prochiral imines.

The synthesis and resolution of an axially chiral benzimidazole-pyridine ligand for the asymmetric reduction of prochiral imines by HSiCl_3 and the addition of allyl- SiCl_3 . The optimization of the ligand for the highest enantiomeric purity of the product. The best ligand will be tested on a set of various model imines to further evaluate the applicability of the proposed catalytic system.



2. State of the art

2.1. Axial chirality

Axial chirality is a special case of chirality in which the molecule does not possess stereogenic center but a chiral axis instead. The chiral axis is an axis about which the set of substituents is held in a spatial arrangement that is not superimposable with its mirror image.¹ There are several types of axially chiral compounds: atropisomeric compounds such as biphenyls **1** or isoquinoline alkaloids² **2**, allenes **3** or various helical structures (such as helicenes or DNA) **4** (**Figure 1**). Since this work deals only with atropisomeric compounds such as **1**, on the main attention will be paid only to those.

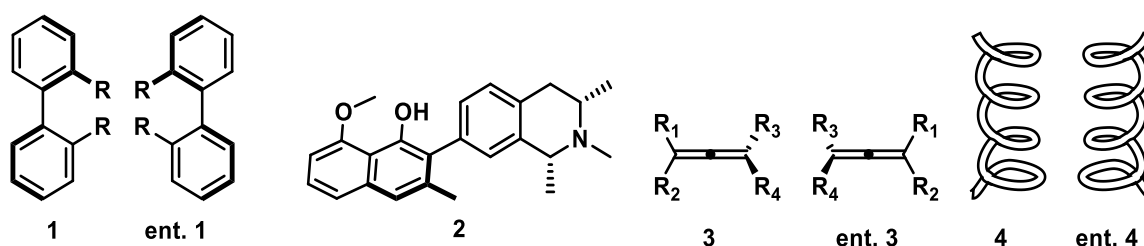


Figure 1 Examples of axially chiral compounds

2.2. Atropisomers

2.2.1. Introduction

Atropisomers are a subgroup of axially chiral compounds, where the chirality is caused by hindered rotation around a single bond in the molecule. Technically, those compounds are conformers with sufficiently high barrier of rotation which allows the isolation of individual conformers.²

The first experimental results from this area come from Christie and Kenner from 1922. They were able to separate axially chiral diphenic acid **5** via crystallization as a brucine salt (**Figure 2**).³

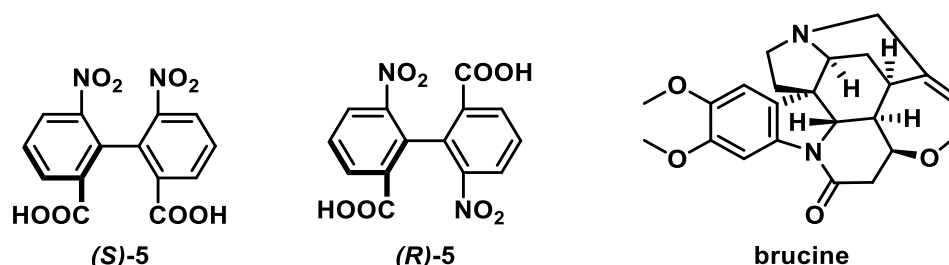


Figure 2 The first resolved atropisomers

Later, Kuhn and Albrecht were able to resolve [1,1'-binaphthalene]-2,2'-dicarboxylic acid **6** using quinine as the resolving agent (**Figure 3**).⁴

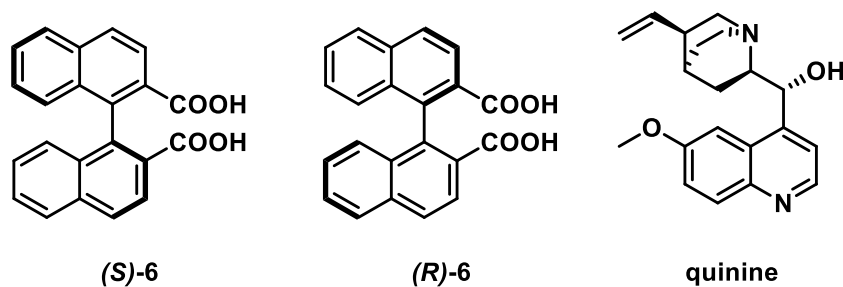


Figure 3 Resolution of 1,1'-binaphthalene derivative

Another early example comes from W. M. Stanley, who was able to resolve 8,8'-dicarboxy-1,1'-dinaphthyl **7** again as a quinine salt (**Figure 4**). Interestingly, 8,8'-diacid **7** is less stable compared to 2,2'-diacid **6**: it took 4.5 hours in a boiling aqueous solution of NaOH to completely racemize **6** while only 30 minutes for diacid **7**, **which** also racemized in aqueous ammonia within 15 hours at room temperature.⁵

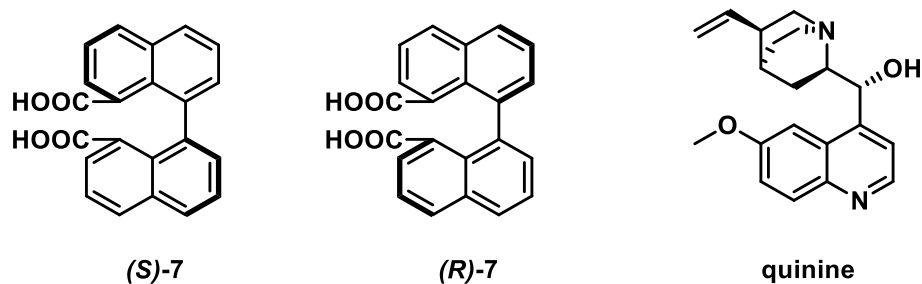


Figure 4 Resolution of 8,8'-binaphthalene derivative

The first examples of 5-membered biaryls come from Adams in 1931. Adams prepared aryl pyrrole **8** and carbazole **9** and was able to resolve them using brucine as a resolving agent.^{6,7}

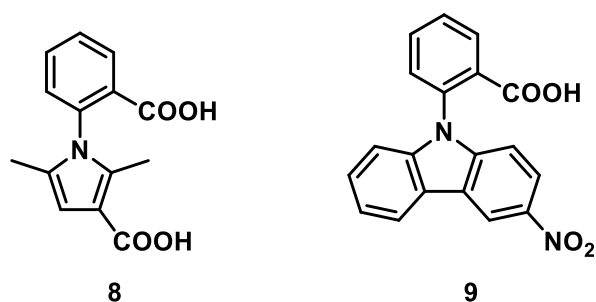


Figure 5 The first examples of 5-membered biaryls

2.2.2. Stability and racemization of atropisomers

Atropisomeric compounds racemize via simple rotation around a single bond. The energy required for this rotation depends on a specific structure of the compound, temperature, or solvent. Atropisomers are generally recognized when their half-life at given temperature is at least 1000 s (17 min). This half-life corresponds to energy barrier of 93 kJ/mol or 22 kcal/mol at 300 K (27 °C).^{2,8} The conformational stability of a compound depends on the following factors²:

- Combined steric demand of the substituents close to the chiral axis
- Existence and structure of bridges
- Presence of racemization mechanism different from simple rotation

Furthermore, the biaryls with two six membered rings such as **5**, **6**, or **7** are more stable than those with one six membered ring and one five membered such as **8**. This is due to the increased distance between ortho substituents next to the chiral axis, which are responsible for the lowering of the rotational barrier.⁹

The effect of ortho substituents was studied by Bott.¹⁰ In general, the rotational barrier increases with the Van Der Waals radius of those substituents: I > Br > Me > Cl > NO₂ > COOH > OMe > F > H and with the number of those substituents (Figure 6). The di-ortho substituted binaphthalene **10** has fairly low rotational barrier of 101 kJ/mol at 317 K (44 °C).^{11,12} The addition of one substituent in biaryl **11**^{13,14} increased the rotational barrier to 125 kJ/mol at 383 K (110 °C) and further addition of ortho-substituents in BINOL **12** increased the rotational barrier up to 158 kJ/mol at 493 K (220 °C).¹⁵ This also explains the results of Kuhn⁴ and Stanley⁵ and why the 2,2'-dinaphthalene dicarboxylic acid **6** (di-ortho substituted) is more stable than 8,8'-diacid **7** (tetra-ortho substituted).

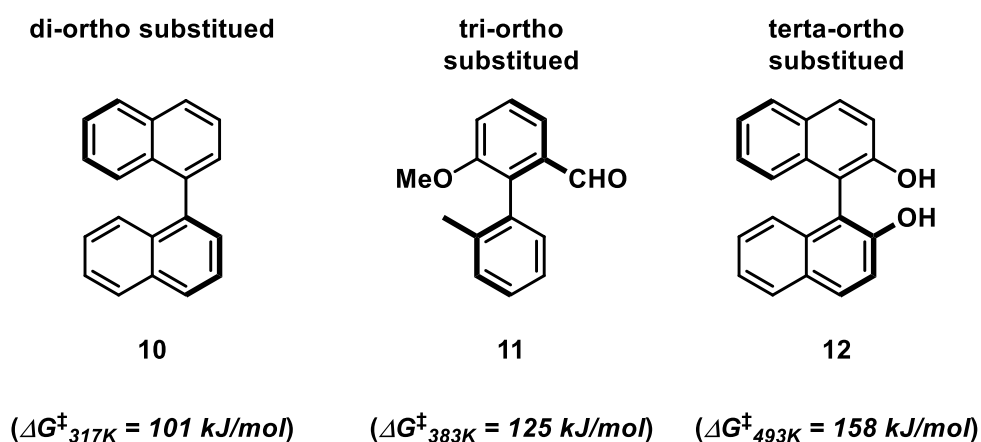


Figure 6 The influence of substituents on the rotational barrier

The presence of a bridge connecting the *ortho*-positions can have a strong influence on the rotational barrier of the biaryl atropisomers. If the *ortho* positions are bridged by one atom bridge, as in compounds **13-15** the rotation is usually not hindered at room temperature.¹⁶

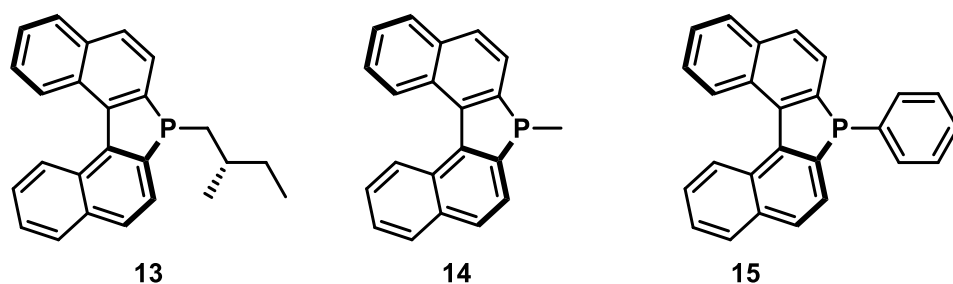
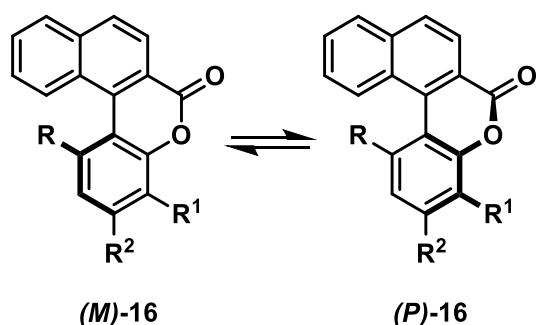


Figure 7 The examples of the *ortho*-bridged atropisomers

The rotational barrier for phosphole **13** was calculated to be 55 kJ/mol at room temperature. This significant instability compared to the unbridged compounds (such as **12**) was explained by the distortion of the binaphthyl ring caused by the presence of the bridge. This caused the protons at positions 8 and 8' to be further apart from each other and thus facilitating the rotation.¹⁶

The presence of the two-atom bridge partially hinders the rotation. The exact magnitude depends on the specific structure of given compound (**Figure 8**).¹⁷ It can be readily acknowledged that the most important substituent in this case is the R substituent in the *ortho* position to the chiral axis. Small substituents (**16a-c, f-h**) have low impact on the rotational barrier and both atropisomers readily interconvert between each other. The more sterically demanding *i*Pr group in **16e** increases the half-life from <1 minute to 28 minutes, while *t*-butyl group further increases the stability to $T_{1/2} = 2.2$ days.



	16a	16b	16c	16d	16e	16f	16g	16h
R	H	OMe	Me	Et	<i>i</i> Pr	H	Me	<i>t</i> Bu
R¹	<i>i</i> Pr	Et	<i>i</i> Pr	<i>i</i> Pr	Me	H	H	H
R²	H	H	H	H	H	H	Me	<i>t</i> Bu
$\Delta G_{298K}^{\ddagger}$ (kJ/Mol)	--	54.4	73.9	83.7	92.3	--	--	104.4
$T_{1/2}$	< ms	0.4 ms	1 s	52 s	28 min	--	--	2.2 d

Figure 8 The effect of the substituents on the racemization kinetics

Derivatives with a three atom bridge show similar stability to the unbridged biaryls¹⁸ and further enlarging of the bridge has similar effects. Interestingly, tripeptide antibiotic biphenomycin A **17**

(**Figure 9**) exists as a single diastereomer, even though there are no ortho-substituents next to the chiral axis.^{19,20}

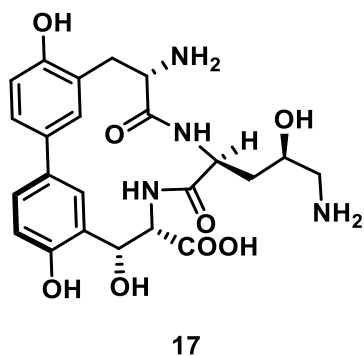


Figure 9 biphenomycin A

In some examples the racemization occurs via more complex mechanism, such as acid catalyzed racemization depicted in **Figure 10**.²¹

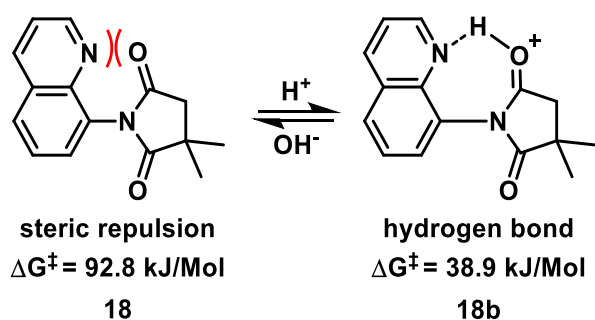


Figure 10 Lowering of the rotational barrier by protonation

The protonation of quinoline **18** caused a significant decrease of the rotational barrier **18b** via a formation of a hydrogen bond. This process was reversible, and an addition of the base stopped this rotation. Another example is an acid catalyzed racemization of BINOL **12**. While BINOL itself is conformationally stable even at elevated temperatures (no racemization occurs after heating under neutral conditions at 100°C for 24 hours), heating in an acidic media (1.2N HCl in dioxane/water) at 100 °C for 24 hours caused complete racemization. The exact mechanism is not known, however cationic species **19** was suggested as the intermediate (**Figure 11**). The presence of sp³-sp² bond instead of original sp²-sp² is likely to facilitate the transformation from **19a** towards **19b**.²²

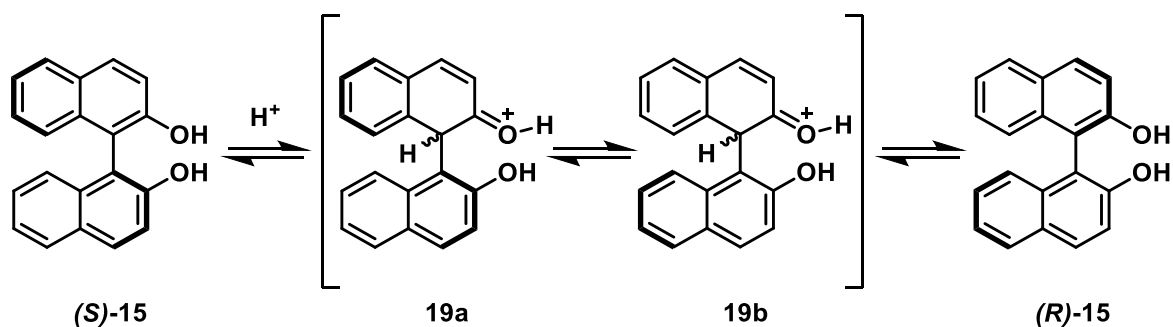


Figure 11 An acid catalyzed racemization of BINOL

In some cases, mere presence of suitable functional groups in the *ortho* position to the chiral axis can induce the racemization. This was described for cyanandione **20** (**Figure 12**).²³ Cyanandione **20**, with a tetra-*ortho* substituted chiral axis, was only isolated as a racemic mixture.²³ The structurally similar hydroxyaldehyde **21** contains the tetra-substituted chiral axis as well and the racemization barrier of **21** is also fairly low: $\Delta G^\ddagger_{296K} = 99$ kJ/mol. This is explained by a formation of hemiacetal **21a** which quickly isomerizes to enantiomer (*P*)-**21**. Methyl-protected derivative **22** is configurationally stable.²⁴

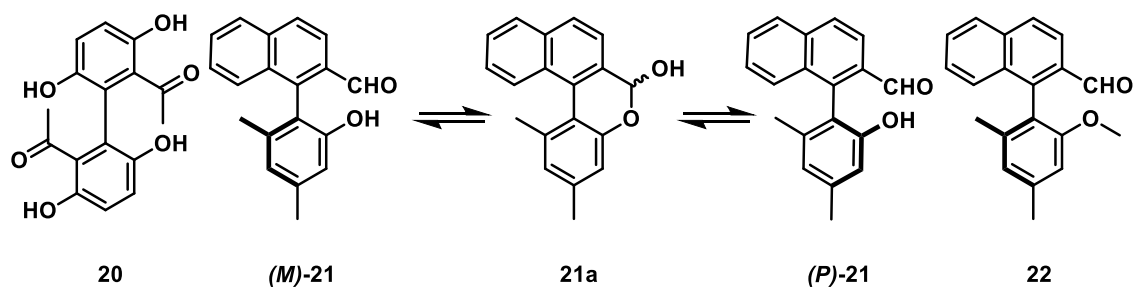


Figure 12 A racemization via a formation of hemiacetal

2.2.3. Synthesis of biaryl atropisomers

The synthesis of biaryl atropisomers can be categorized into two main approaches: a) synthesis of a racemate followed by a resolution or b) atroposelective synthesis. The racemic synthesis uses common arylation reactions such as Suzuki coupling, Buchwald-Hartwig amination, Ullmann coupling, or Chan-Lam coupling. The cyclization reactions are usually followed by a resolution using common methods such as crystallization or chiral HPLC. The atroposelective synthesis is rather complicated because it requires a formation of a sterically hindered bond, which may require harsher conditions (e.g. higher temperatures). These conditions may frequently cause a negative effect on stereoselectivity of the reaction.² Some of the developed methodologies (**Figure 13**) are briefly reviewed in this chapter.

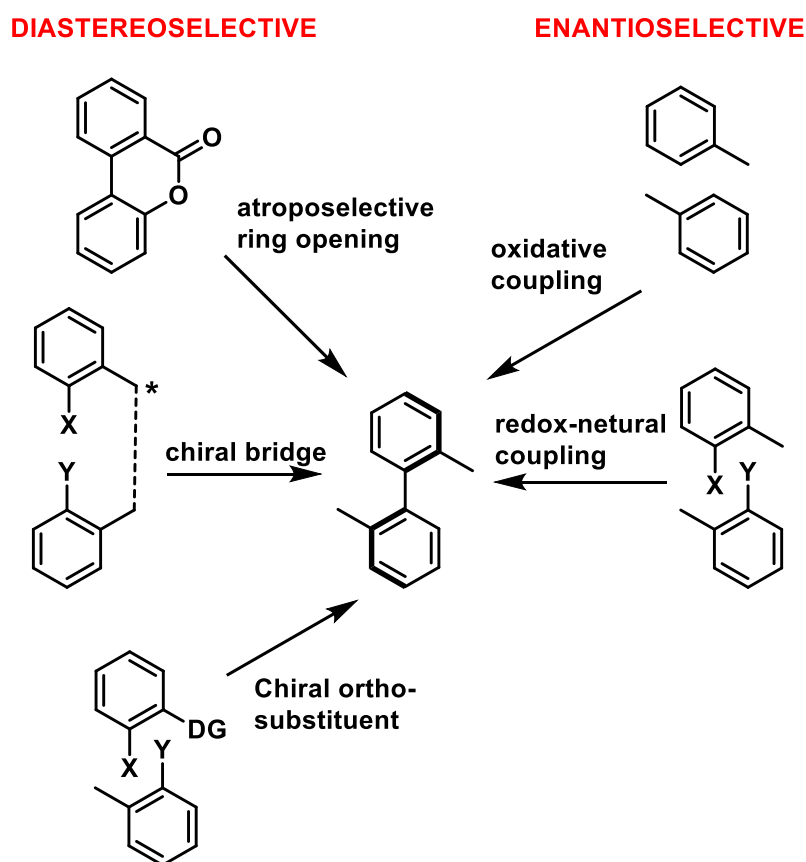
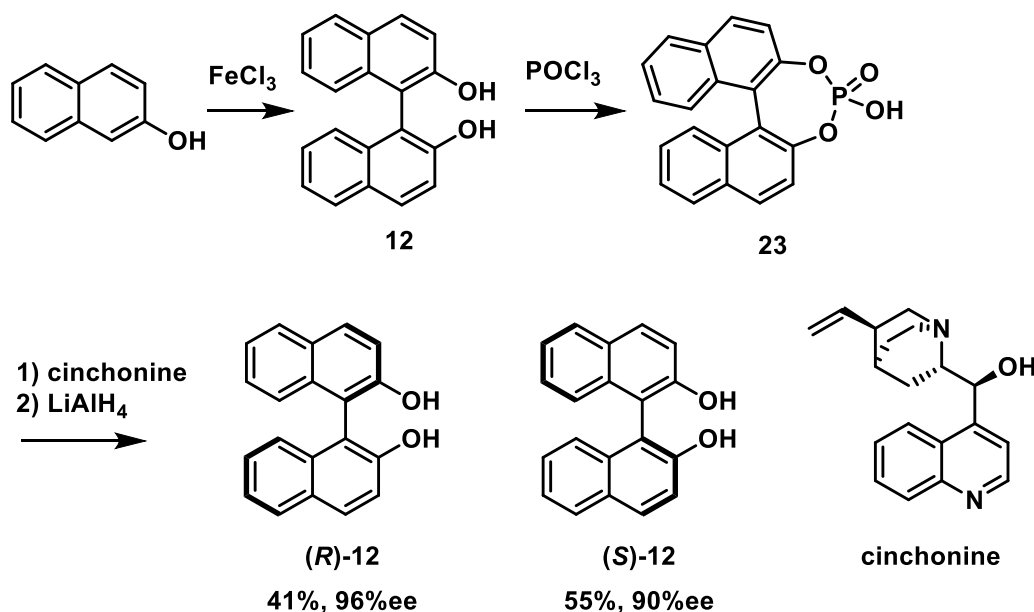


Figure 13 Synthetic strategies leading to the atropisomeric biaryl compounds

2.2.3.1. Oxidative coupling

BINOL **12** can be prepared by the oxidative coupling of naphthalen-2-ol using various metal oxidants, such as FeCl_3 .²⁵ BINOL can be resolved *via* cinchonine salt after the conversion to phosphoric acid ester **23** (**Scheme 1**). After LiAlH_4 reduction, (*R*)-BINOL was isolated in 41% yield and 96% ee while (*S*)-BINOL was isolated in 56% yield and 90% ee.²⁶ The procedure was further modified with 2-

aminobutanol in the resolution step to improve the optical purity to >99 % ee. Unfortunately the yields were reduced to 30 % and 15 %.²⁷



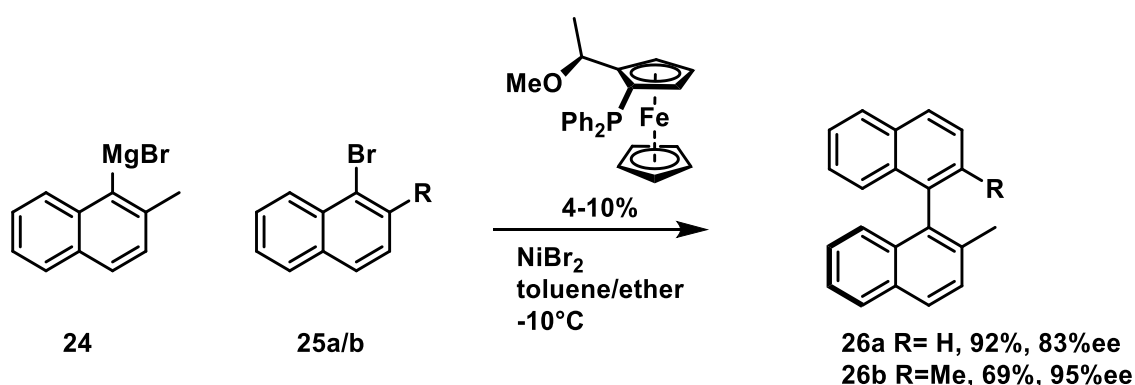
Scheme 1 Synthesis and resolution of BINOL

While the resolution methods allowed for synthesis of both enantiomers of BINOL, atroposelective oxidative coupling was explored because it would not require the resolution step. The first synthesis used Cu(NO₃)₂ as an oxidant together with (*S*)-phenethylamine as a chiral ligand to prepare BINOL in 63% yield and only 3% ee.²⁸ Further optimization of chiral ligand increased the enantioselectivity to 96% ee and the yield to 94 %.²⁹ However, the large excess of a chiral salt (8 equivalents) was needed. This was solved by Smrčina and Kočovský, who developed a procedure using one equivalent of the Cu-sparteine complex. This method allowed the atroposelective synthesis of unsymmetrical biaryls as well. The reaction was optimized for the synthesis of BINOL which was obtained in excellent enantioselectivity (>99% ee) but only modest yield (36 %).³⁰ Further modification included enzymatic resolution or the use of different resolving agents, which were thoroughly reviewed by Brunel.³¹

2.2.3.2. Redox-neutral coupling

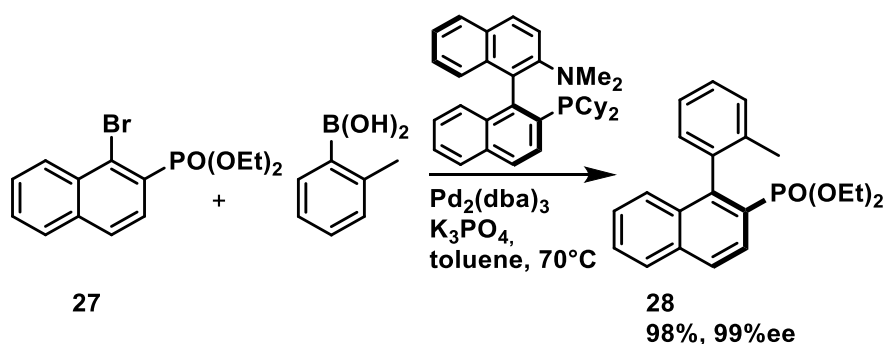
Unlike oxidative couplings, atroposelective redox-neutral couplings offer several advantages. The biggest are zero requirements for the specific substitution patterns and the option for regioselective coupling of two different aromatics. This allows simple synthesis of various biaryls which are lacking specific functional groups required for oxidative coupling. The first atroposelective example of redox-neutral coupling was performed by Hayashi in 1988 (**Scheme 2**).³² The Grignard reagent **24** was coupled together with various aryl bromides **25a-b** under mild conditions using a chiral Ni catalyst. Products

26a-b were isolated in good yield and enantioselectivity. Various ligands for asymmetric Kumada coupling were also screened, however, with low success.^{33,34}



Scheme 2 An atroposelective Kumada coupling

The first examples of atroposelective Suzuki-Miyaura coupling come from groups of Crépy³⁵ and Buchwald.³⁶ Crépy obtained various biaryls with enantiomeric excess between 5 and 85 %. Interestingly, the use of pinacolboranes gave opposite configuration of the product compared to free boronic acid or ethylene glycol esters. Buchwald used phosphonate-substituted naphthyl halide **27** as a coupling partner. This proved beneficial and products were isolated in high yields and % ee using axially chiral biaryl ligands (**Scheme 3**). The use of a phosphonate ester in the *ortho* position was crucial for high enantioselectivity and it was further transformed by Grignard reaction followed by a reduction into phosphine derivatives, which could be used as chiral ligands.



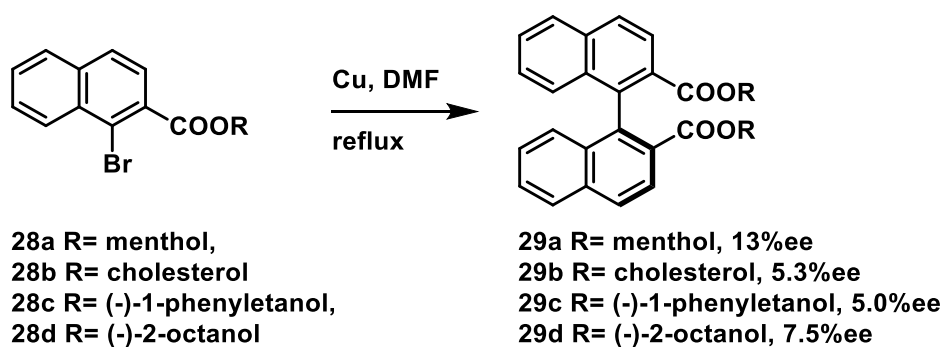
Scheme 3 An atroposelective Suzuki coupling

2.2.3.3. Use of a chiral directing group

The use of a chiral directing group is another approach for the synthesis of axially chiral biaryls. Compared to the oxidative and redox-neutral couplings, it offers one distinctive advantage: the products are formed as a diastereomeric mixture, which subsequently allows for easier separation *via*

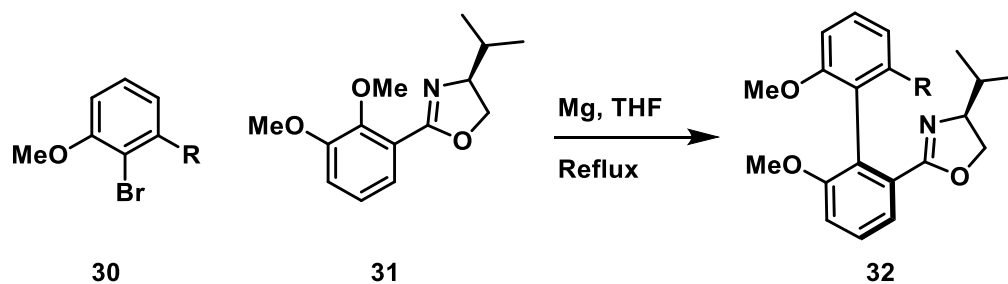
crystallization or column chromatography. In most cases, the chiral auxiliary group needs to be removed afterwards. This may lower the overall yield or even cause a partial racemization.

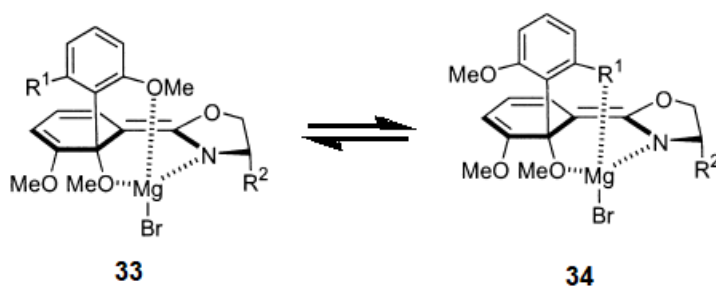
The first example of a chiral directing group in the *ortho*-position comes from Miyano who coupled chiral esters of 1-bromo-2-naphthoic acid esters **28a-d** under Ullmann conditions (**Scheme 4**) to yield various binaphthyls **29a-d**.³⁷ Yields were high, up to 93 %, however, the enantioselectivity was poor.



Scheme 4 Diastereoselective Ullmann coupling

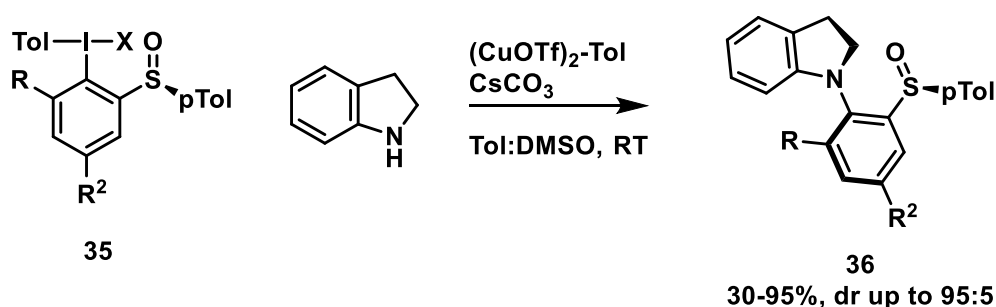
This methodology was improved by Meyers, who used aryl Grignards and methoxy-phenyl oxazolines in S_N2 -Ar type reaction (**Scheme 5**).^{38,39} Required oxazolines can be easily prepared from benzoic acid and amino alcohols^{40,41} by various methods. The stereoselectivity of the reaction highly depends on the structure and coordination ability of the “R” group compared to the methoxy group. In the case, where the R group is only weakly or not at all coordinated to magnesium (R= Me, OTBS), the methoxy group is coordinated to magnesium and directs the orientation of the aryl ring (**Scheme 5**, **33**). The product can be subsequently obtained in high % ee. In the other case, where the “R” group is coordinated stronger than the methoxy group (R= 1,3-dioxolan-2-yl), the proposed coordination **34** rotates the aryl ring in an opposite direction. The product with reversed configuration is obtained in high chiral purity. At the edge case, where the “R” group has similar coordinating properties as OMe group (R= OBn), the product with low chiral purity is obtained, due to a low preference for given transition state **33** or **34**.





Scheme 5 Oxazoline-directed atroposelective arylation (taken from ref. ³⁹)

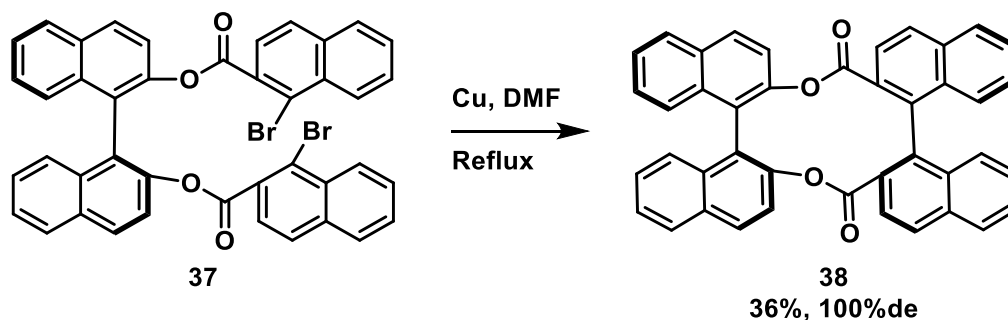
While those methods are robust and work well to prepare biphenyl or binaphthyl type of atropisomers, the synthesis of C-N biaryl atropisomers are far less developed. This might be due to the Ullmann and Buchwald-Hartwig reactions requiring more forcing conditions compared to oxidative couplings or Grignard reactions. This was partially solved by Colobert by use of chiral sulfinyl iodanes **35** and copper catalysis (**Scheme 6**) to prepare atropisomeric *N*-aryl indolines **36** in high enantiomeric purity and yield.⁴² While there are other reported atroposelective syntheses of C-N atropisomers, either biaryls⁴³⁻⁴⁶ or other types^{47,48} this is the only example that features direct *N*- arylation to form the chiral axis in the same step we found in the literature.



Scheme 6 An atroposelective synthesis of *N*-aryl indoline

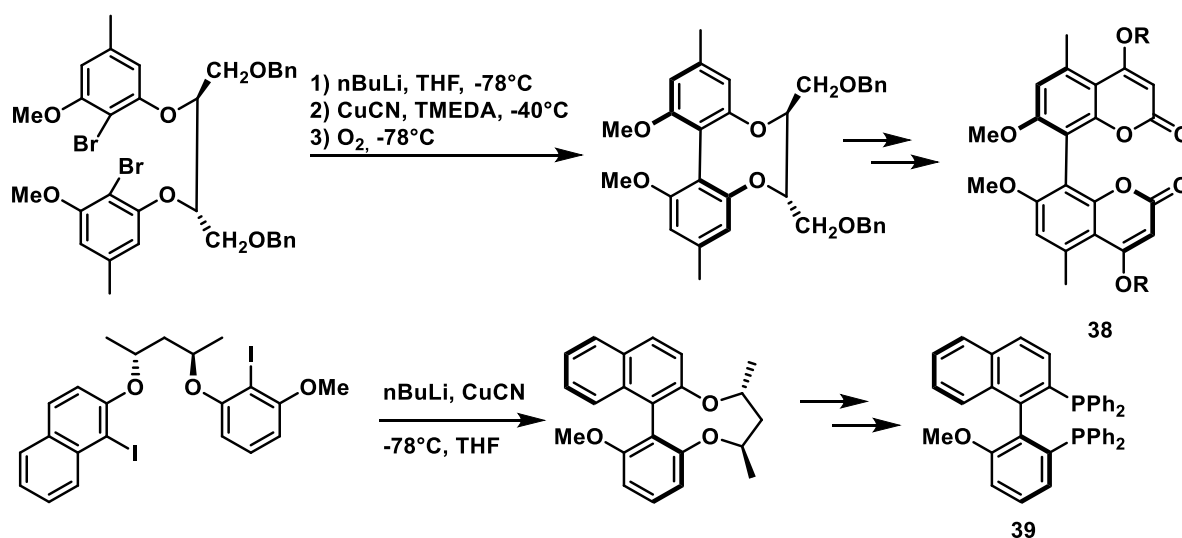
2.2.3.4. Chiral bridge mediated synthesis

The use of a chiral bridge provides another synthetic tool leading to the atropisomers. Unlike the previous method, the two coupling partners are connected by a chiral bridge. This allows high yields of intramolecular coupling and options to prepare both symmetrical and asymmetrical biaryls. This approach was pioneered by Miyano (**Scheme 7**).^{49,50} While forcing conditions were used (Ullmann coupling, refluxing DMF), the chiral tether allowed higher chiral purity of products compared to intermolecular Ullmann coupling (**Scheme 4**). The use of BINOL as a chiral tether was critical to ensure high enantiomeric purity, although the yields were lower in some cases (36-80 %, mostly around 40 %).



Scheme 7 Atroposelective synthesis of BINOL directed by chiral bridge

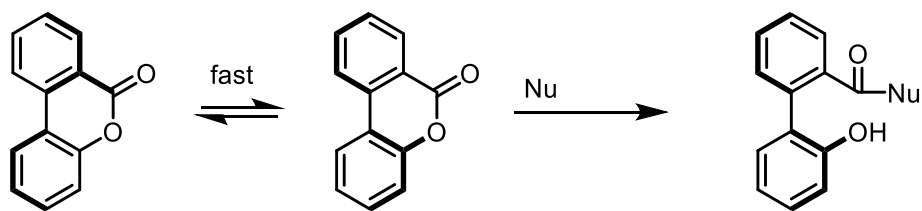
Further improvements were made by Lipshutz who used a cyanocuprate coupling that allowed to use lower temperatures⁵¹ and introduced diether tethers⁵² which were used with high success in total synthesis of natural products such as (+)kotanin **38**⁵³ or in a synthesis of chiral biaryl ligand NAPhePHOS **39** (Scheme 8).⁵⁴



Scheme 8 Chiral bridge directed biaryl synthesis

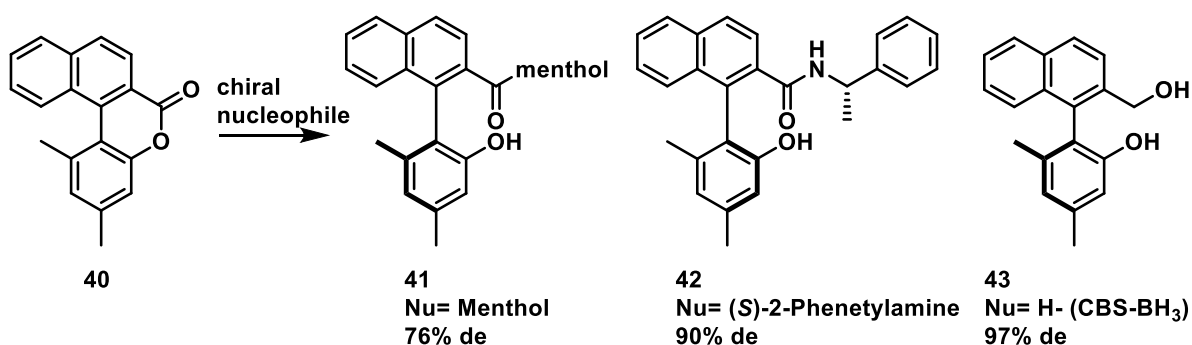
2.2.3.5. Atroposelective ring opening

As mentioned in a previous chapter, biaryls bridged with two atom bridge (**Figure 8**, **Figure 12**) are not conformationally stable and – depending on an exact structure – quickly convert between each other. This instability can be exploited, assuming one can open the lactone bridge with a suitable chiral nucleophile (**Scheme 9**) which leads to dynamic-kinetic resolution.



Scheme 9 Diastereoselective ring opening

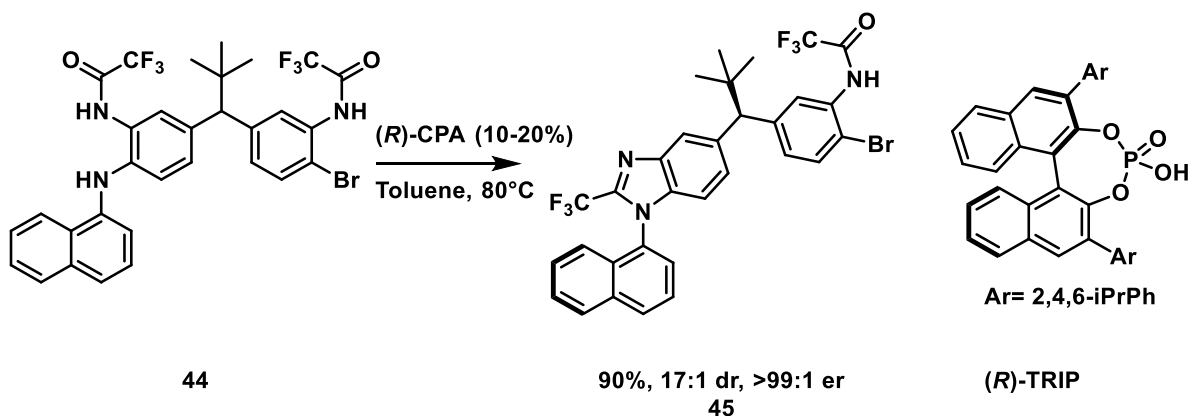
Various nucleophiles ranging from sodium salts of menthol **41**, its derivatives,⁵⁵ or phenethylamine **42**,⁵⁶ to hydride using BINAL-H⁵⁷ or CBS-borane catalyst **43**^{58,59} were used to stereoselectively open the lactone **40** (**Scheme 10**).



Scheme 10 Diastereoselective ring opening

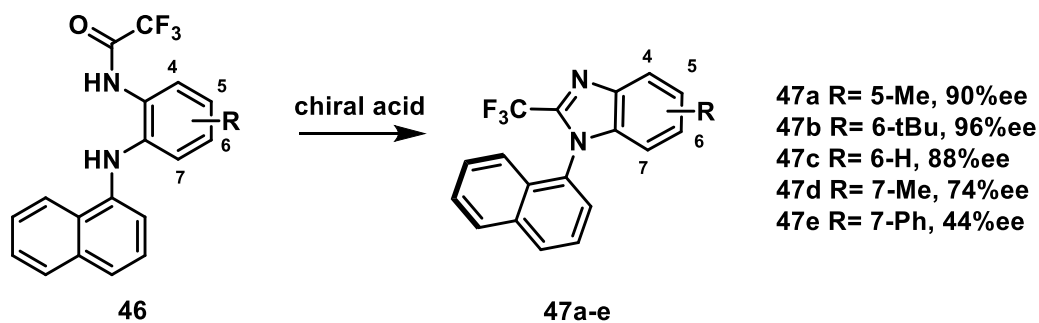
2.2.3.6. Atroposelective ring closing reactions

Atroposelective ring closing reactions provide an alternative approach; however, they are limited towards the synthesis of heterocyclic biaryls due to the ease of ring closing reactions. Recent example comes from the Miller group (**Scheme 11**).⁴⁵



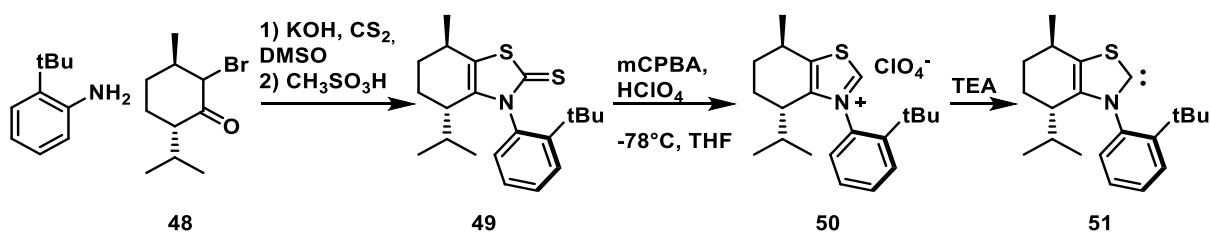
Scheme 11 Atroposelective cyclodehydration

The use of the chiral acid allowed to form trifluoromethylbenzimidazole **45** from a precursor **44** in a high yield and diastereomeric excess as a single enantiomer. Various other BINOL-derived phosphonic acids were used as well and the scope was broadened in the follow-up study.⁴⁶ Various substituted phenylenediamines **46** were subjected to cyclization with chiral acids to yield axially chiral benzimidazoles **47a-e** in high yields and enantiomeric excess (**Scheme 12**). Unfortunately, the methodology is limited to trifluoroacetamides and it is not clear if the less electrophilic amides could be used.



Scheme 12 Atroposelective cyclodehydration

A different cyclization was utilized by Pesch who used a chiral 2-bromomenthone **48** as a starting material for a synthesis of axially chiral thiazole **49**. Compound **49** was obtained as a single diastereomer after the crystallization. Thiazole **49** was further oxidized by mCPBA in a presence of HClO₄ to yield the thiazolium salt **50** which was converted by a treatment with triethylamine into the atropisomeric *N*-heterocyclic carbene **51** (**Scheme 13**). Carbene **51** was used as a catalyst for the asymmetric Strecker reaction and benzoin condensation.⁶⁰ Unfortunately, while the thiazolium precursor **50** was atropisomerically stable, the carbene **51** partially racemized during the reaction and was therefore proved unsuitable as a catalyst.



Scheme 13 A synthesis of an axially chiral NHC

2.3. Assignment of the absolute configuration by NMR

2.3.1. Introduction

The absolute configuration is one of the key characteristics of chiral compounds. There are several methods that allow the configuration assignment. Those are for example chiroptical methods⁶¹ or X-ray crystallography,⁶² however, the high availability of NMR instrumentation makes it the competitive choice.

Chiroptical methods such as vibrational circular dichroism (VCD) or optical rotary dispersion (ORD) require considerable time to perform required calculations and simulations of the spectra, which are then compared to experimentally obtained ones. Those calculations become more difficult if the compound of interest is flexible. On the other hand, chiroptical methods are nondestructive, do not require chemical modifications and therefore allow analysis of compounds with no suitable functional groups.⁶¹

X-ray crystallography is a robust method, however, the main limitation is the requirement of high-quality monocrystal which might take considerable amount of time and effort to prepare, even though there are numerous manuals and guides available.^{63,64} A significant improvement such as crystalline sponge⁶⁵ or a formation of guanidinium co-crystals have been reported recently.⁶²

NMR spectroscopy can be used provided that several criteria are met. The most important is the presence of suitable functional groups that allow the modification of the analyte with a suitable chiral reagent. This modification can be either noncovalent using chiral solvating agents (CSA) or covalent using chiral derivatization agents (CDA). Since the experimental work described in this thesis deals with a development of new CDA, this chapter will focus on the applications of various CDAs.

Theoretically, any chiral compound can be used as a CDA because covalent modification of given chiral analyte with chiral CDA will lead to diastereomeric compounds if the different enantiomers of CDA are used. The diastereomers will differ in their NMR spectra, unlike enantiomers. For the compound to be used as a reliable CDA, the NMR difference in spectra of prepared diastereomers needs to be predictable. This would lead to the assignment of the correct configuration of the analyte. This requirement disqualifies most of the chiral compounds. The “ideal” CDA should possess the following structural features:⁶⁶

- a) A suitable functional group that allows the covalent modification of the analyte – most often carboxylic acid, but alcohols or amines could be used as well.
- b) A suitable functional group that projects the anisotropic effect on the analyte which causes the predictable change of NMR spectra (“shielding effect”) - most often an aromatic ring such as phenyl or anthryl.

- c) A suitable polar group which “locks” the compound in a preferred conformation which allows the selective projection of the shielding effect on specific substituents of the analyte.

The structure of general CDA **52** is depicted in **Figure 14**. The X-group allows the modification of the analyte, Y-group projects the shielding effect towards the substituents R³ **53** and R⁴ **54** in the analyte. This causes the selective change in the NMR spectra. R¹ and R² are other functional groups which play a role in the maintaining of the specific conformation of the diastereomers **53** and **54**.

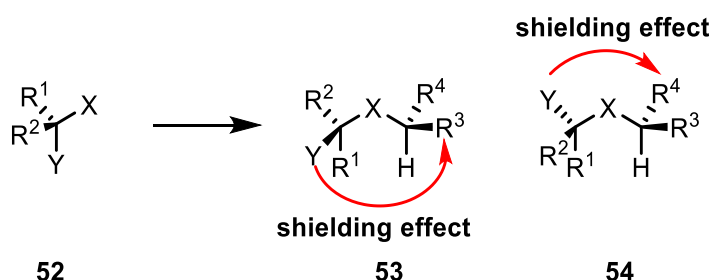
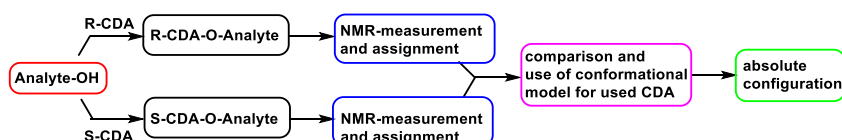


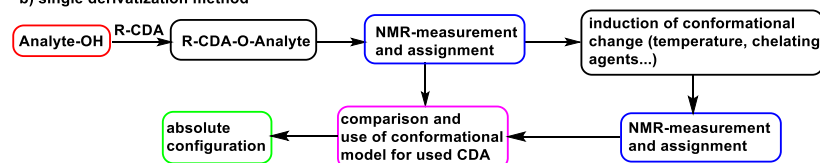
Figure 14 Schematic representation of the principle of the method

Most commonly, the analyte is modified separately with both enantiomers of the CDA and their NMR spectra are compared (Double derivatization method, **Figure 15a**). It is also possible to analyze only a single diastereomer and compare the spectra measured at different temperature or after addition of an additive which causes a conformational change (Single derivatization method, **Figure 15b**).⁶⁷ The last and most limited is a comparison of the NMR spectra of CDA modified analyte with the spectra of unmodified analyte. In all those cases, two different NMR spectra are measured and compared (Single esterification method, **Figure 15c**).

a) double derivatization method



b) single derivatization method



c) single esterification method

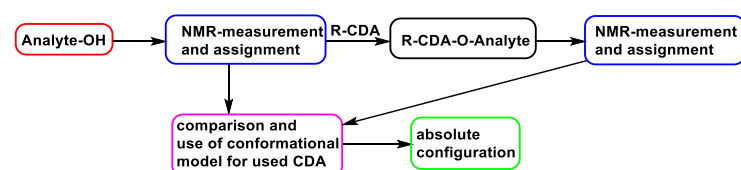


Figure 15 Approaches towards the configuration assignment by NMR

The range of substrates includes α -chiral secondary alcohols^{68,69} and amines⁷⁰, β -chiral primary alcohols,^{68,71} cyclic secondary amines,^{72,73} tertiary alcohols,^{74,75} thiols,⁷⁶ cyanohydrins⁷⁷⁻⁷⁹ or polyfunctional amino alcohols.^{80,81} While the substrate scope is fairly broad, it is important to know that not every CDA is suitable for each of those analytes.

2.3.2. Analysis of chiral secondary alcohols

2.3.2.1. Mosher's acid

Methoxy(trifluoromethyl)phenylacetic acid (MTPA) commonly known as Mosher's acid **55** (**Figure 16**) is the most frequently used acid since its first description by Dale and Mosher in 1973.⁸²⁻⁸⁴ Analytes can be acylated with MTPA and a suitable activator or directly with acid chloride MTPA-Cl **56**. It is important to note that while the acid and chloride have the same spatial arrangement of substituents, the CIP priority is different - (*S*)-acid (*S*)-**55** provides the (*R*)-chloride (*R*)-**56**.

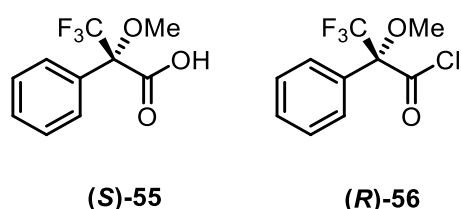


Figure 16 Structure of Mosher's acid

First, ¹⁹F NMR was used by Mosher⁸³ with an advantage due to the simplified interpretation of the ¹⁹F spectra at the time. The proposed conformational model, which allows the assignment, is shown in **Figure 17**.

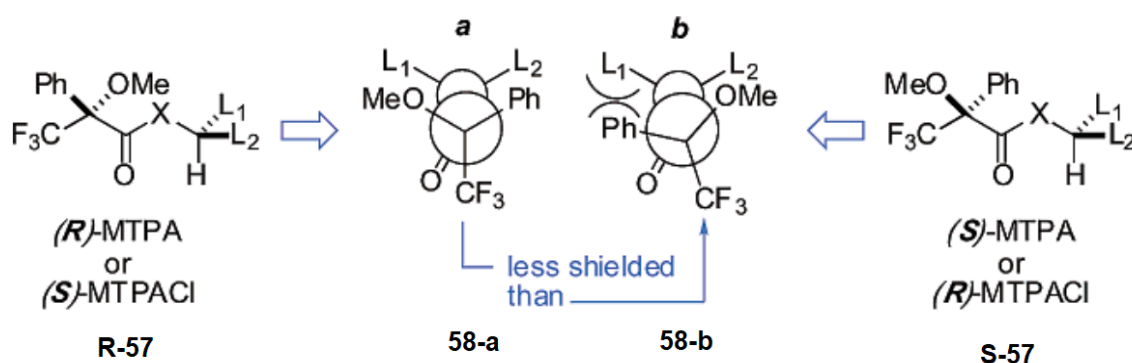


Figure 17 Conformational model used for the configuration assignment on the basis of the ¹⁹F spectra (taken from ref. ⁸⁵)

Mosher assumed the preferred conformation being the one depicted in **Figure 17 (R)-57 or (S)-57**. The proton at the chiral carbon, carbonyl oxygen, and trifluoromethyl group are in *syn*-periplanar conformation. Assuming L^1 substituent is bulkier than L^2 , when the phenyl ring is on the same side as the bulkier substituent L^1 (**Figure 17, 58-b**) the steric interaction causes the distortion of the conformational equilibria and a slight rotation which moves the CF_3 group into the shielding zone of the carbonyl oxygen. This results in a lower ^{19}F chemical shift compared to **58-a**. This shielding can be expressed as a parameter $\Delta\delta^{SR}(^{19}F)CF_3$ which can be calculated by subtracting the ^{19}F chemical shift of the (*R*)-MTPA ester from the (*S*)-MTPA ester: $\Delta\delta^{SR}(^{19}F)CF_3 = \delta CF_3(S) - \delta CF_3(R)$. In the case of alcohol with a configuration as depicted in **Figure 17** (assuming L^1 is bulkier than L^2), the resulting calculation yields $\Delta\delta^{SR}(^{19}F)CF_3 < 0$. If the alcohol had an opposite configuration, the resulting analysis would yield $\Delta\delta^{SR}(^{19}F)CF_3 > 0$. While the use of the ^{19}F NMR allows straightforward assignment due to a low number of signals in the spectra, this method was later rejected due to its low reliability.⁸⁶

The use of the 1H NMR is more common than the use of the ^{19}F . The greatest advantage of 1H over ^{19}F NMR lies in the number of data points gathered. The ^{19}F NMR always gives one or the other configuration and because only one signal is obtained, there is no room for self-correction. On the other hand, most organic molecules contain multiple protons. Those can be analyzed, and any anomalous behavior can be revealed. The conformation model for the use of 1H NMR is different compared to the ^{19}F NMR and shown in **Figure 18**.⁸⁵

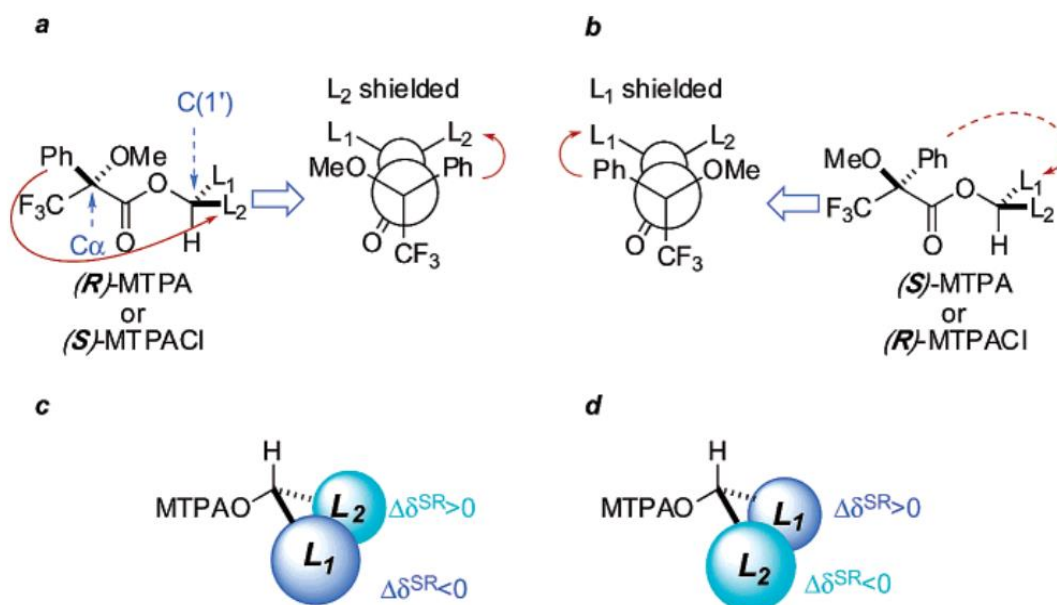


Figure 18 Conformational model for the absolute configuration assignment of a chiral alcohol by Mosher's acid (taken from ref. ⁸⁵)

The conformation is the same however the shielding effect is caused by the phenyl rings and is projected towards one of the substituents (either L^1 or L^2). If (*R*)-MTPA is used, the shielding is

projected towards the L² substituent (**Figure 18a**) whilst when the opposite enantiomer (*S*)-MTPA is used, the shielding is projected towards the L¹ substituent (**Figure 18b**). This shielding is opposite if the alcohol has opposite configuration. The shielding towards the substituents can be calculated in a similar fashion as in the case of the ¹⁹F spectra:

$$\Delta\delta^{\text{SR}}(\text{L}^1) = \delta\text{L}^1(\text{S}) - \delta\text{L}^1(\text{R})$$

$$\Delta\delta^{\text{SR}}(\text{L}^2) = \delta\text{L}^2(\text{S}) - \delta\text{L}^2(\text{R})$$

Due to the shielding depicted in this example:

$$\Delta\delta^{\text{SR}}(\text{L}^1) < 0$$

$$\Delta\delta^{\text{SR}}(\text{L}^2) > 0$$

After the calculation is performed, the spatial arrangement of substituents L¹ and L² can be decoded using the simplified models shown in **Figure 18c/d**. Naturally, all protons located in L¹ or L² substituent should have the same sign of the $\Delta\delta^{\text{SR}}$ and it is advised to calculate as many $\Delta\delta^{\text{SR}}$ parameters for as many protons as possible because of higher reliability of such assignment. ¹³C NMR analysis can be performed in the same manner as ¹H.⁸⁷

Unfortunately, MTPA suffers from several limitations that complicate the structural assignment of MTPA esters or amides:

- The $\Delta\delta^{\text{SR}}$ differences are often not high enough to be safely used.
- Anomalous values are often observed.

The selection of compounds, which do not follow the proposed models, is shown in **Figure 19**.

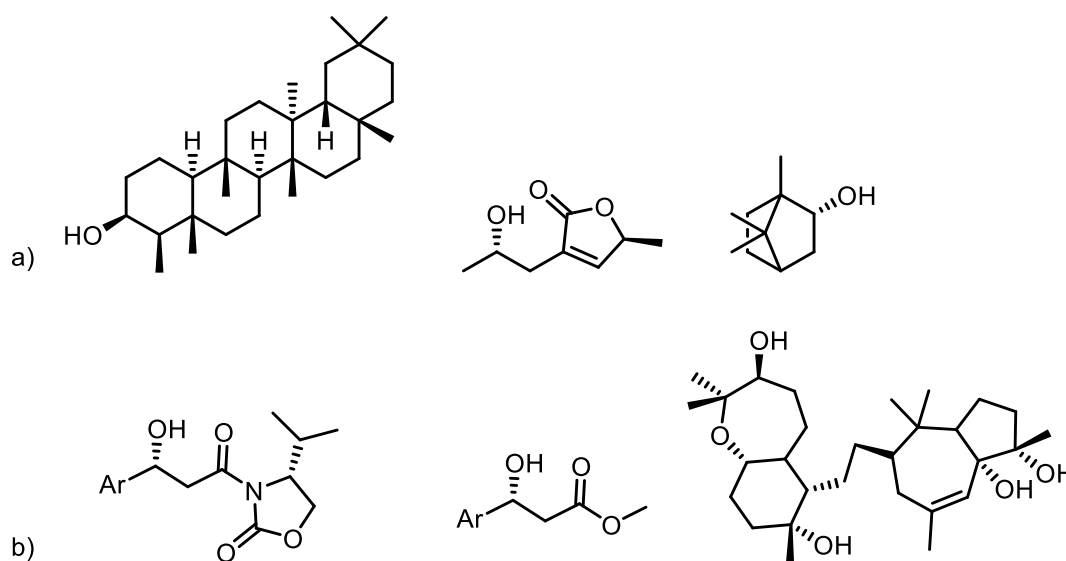


Figure 19 The examples of compounds that do not follow models developed for Mosher's acid
a) compounds that do not follow ¹⁹F model b) Compounds that do not follow ¹H model

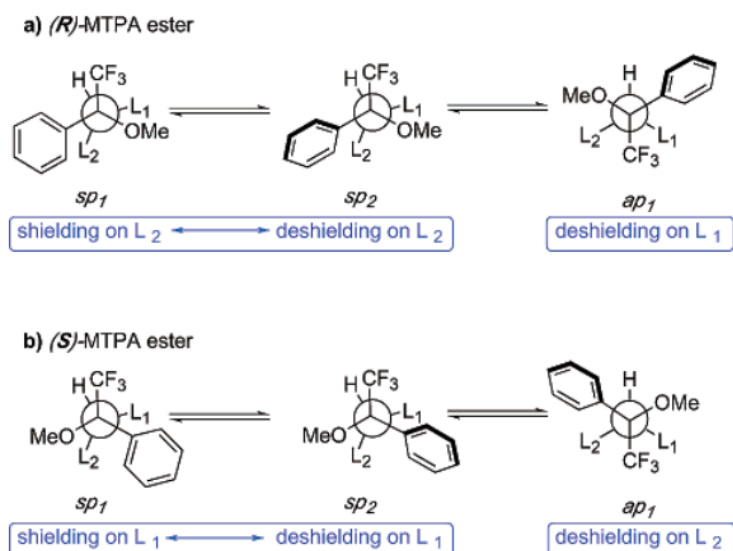


Figure 20 Major MTPA conformers and their shielding effects (taken from ref. ⁸⁵)

These anomalies in MTPA assignment were further reinvestigated using computational methods.⁶⁸ It was revealed that the conformational equilibrium is more complex than was assumed by Mosher. It was revealed that MTPA exists in three conformers which produce different shielding and deshielding effects and are in a delicate balance with each other (**Figure 20**).

The *sp*₁ conformer of (*R*)-MTPA esters (**Figure 20a**) was assumed by Mosher and produces the shielding effect on substituent L² in accordance with the proposed model. The *sp*₂ conformer which is caused by a simple rotation around C_{AR}-C bond produces the deshielding effect on the same substituent, therefore limiting the magnitude of observed $\Delta\delta^{\text{SR}}$. Further rotation around C-C_{carbonyl} creates conformer *ap*₁ which produces the deshielding effect on a substituent L¹. Those major conformers are in balance which can be distorted by a change of experimental conditions – such as concentration or temperature which therefore causes the irregularities in the observed $\Delta\delta^{\text{SR}}$ values.

2.3.2.2. Methoxyphenylacetic acid

Methoxyphenylacetic acid **58** (MPA, **Figure 21**) was also reported by Mosher.⁸⁴ Its application was limited due to the observed racemization during the acylation step. These difficulties were later solved by Trost⁸⁸ by the use of different acylation conditions.

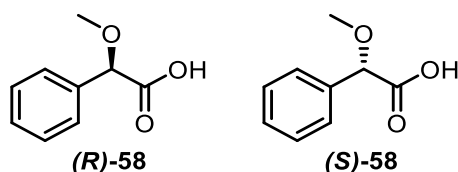


Figure 21 The structure of the methoxyphenylacetic acid (MPA)

The proposed conformational model⁸⁵ is depicted in **Figure 22**: the methoxy, carbonyl and C₁H groups are in a *syn*-periplanar conformation which allows the phenyl ring to produce shielding effect towards one of the substituents L¹ or L² (**Figure 22a**). The shielding parameter $\Delta\delta^{RS}$ is calculated analogously as in the case of MTPA and based on the $\Delta\delta^{RS}$ values (**Figure 22b**). Importantly MPA and other CDAs use the opposite convention than MTPA to describe the shielding effect: $\Delta\delta^{RS}$ instead of $\Delta\delta^{SR}$. $\Delta\delta^{RS}$ is calculated using the similar procedure: $\Delta\delta^{RS}(L) = \delta L(R) - \delta L(S)$. It was noted that this convention is often overlooked, and some publications use the MTPA calculation method.

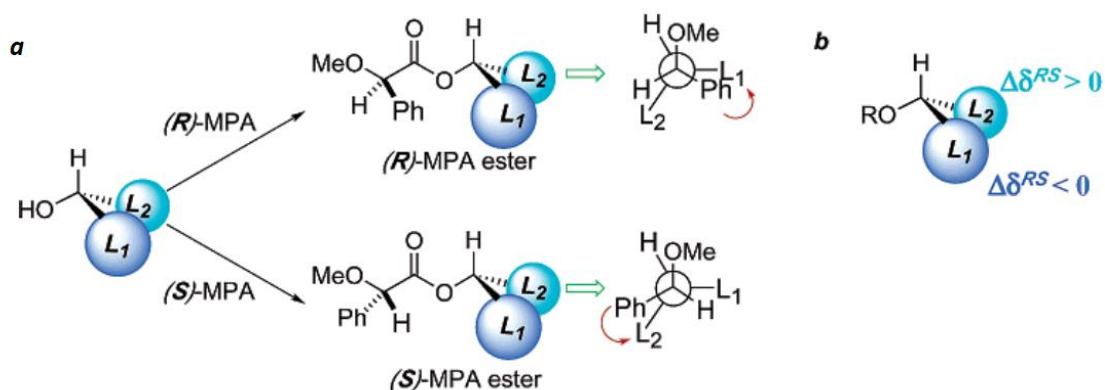


Figure 22 Conformational model for the configuration assignment of the alcohols using MPA (taken from ref. ⁸⁵)

The conformation equilibrium of the MPA is significantly simpler compared to the MTPA: only two major conformers were described⁸⁹ which are depicted in **Figure 23**.⁸⁵

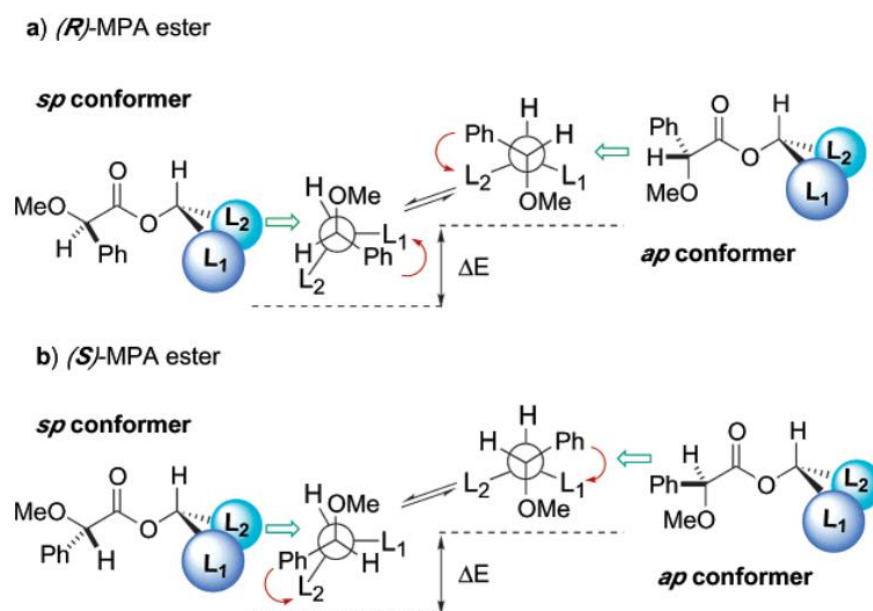


Figure 23 Major conformers of MPA esters (taken from ref. ⁸⁵)

The major conformer, *sp*, contains methoxy group, carbonyl, and proton in the *syn*-periplanar conformation. This conformation allows the phenyl ring to project the shielding effect towards L¹

(**Figure 23a**). The minor conformer, ap, which is approx. 1 kcal/mol less stable, is formed by the rotation of the C-C bond between the carbonyl carbon and carbon in position 2. In this case, the phenyl ring projects the shielding effect towards substituent L². The shielding effect on L² is weaker because the phenyl ring and L¹ are not exactly aligned. The combination of higher stability of sp conformer and the weaker shielding on opposite substituent in the ap conformer, leads to higher observed $\Delta\delta^{\text{RS}}$. The same conformational model can be used for the analysis of thiols, however, smaller $\Delta\delta^{\text{RS}}$ are observed.⁷⁶

2.3.3. Other arylmethoxyacetic acids

Further modifications of the structure of MPA were performed. At first, a change of the methoxy group to other alkyls or acyls was attempted.⁹⁰ However, this modification did not provide any significant improvement and, in most cases, the $\Delta\delta^{\text{RS}}$ differences were smaller compared to MPA. Further modification consisted in the exchange of the phenyl ring for different aryls.^{89,91} The examples of the arylmethoxyacetic acids are shown in **Figure 24**

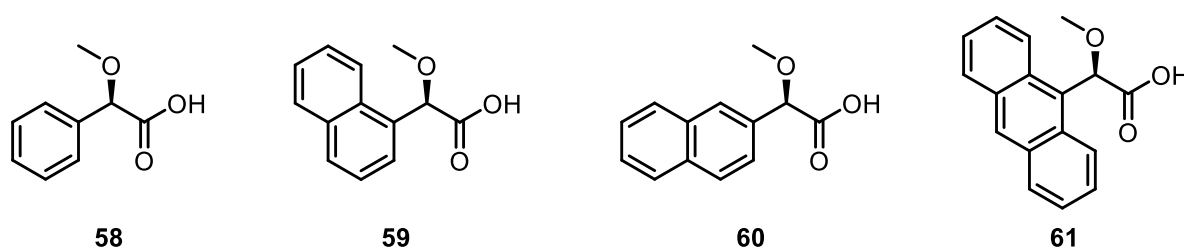


Figure 24 (R)-MPA **58**, (R)-1-NMA **59**, (R)-2-NMA **60** and 9-AMAA **61**

The most promising structure is 9-AMAA **61** which showed the most significant $\Delta\delta^{\text{RS}}$ differences as can be seen in **Figure 25**. Three model substrates 3,3-dimethylbutan-2-ol **62**, 1-phenylethanol **63**, or menthol **64** were compared.⁸⁹

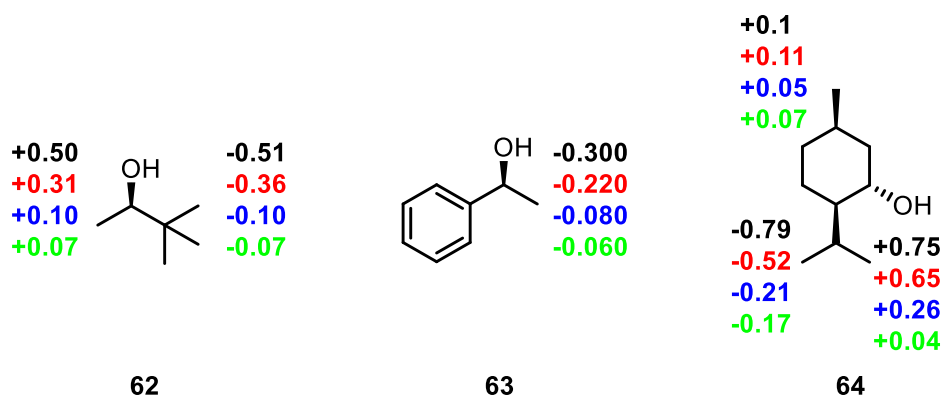


Figure 25 A comparison of $\Delta\delta^{\text{RS}}$ differences between 9-AMAA, 1-NMA, MPA, and MTPA

There is a difference between MTPA and MPA in the magnitude of the $\Delta\delta^{\text{RS}}$ parameter as can be seen in **64**, however, the substitution of the phenyl ring for larger rings such as naphthyl in 1-NMA or anthryl in 9-AMAA shows significant improvement in the differentiation of the signals of interest as can be seen in **62**, **63**, **64**. The substitution of the aromatic moiety plays dual role: first, the larger aromatic ring is able to project the shielding effect towards larger area. Second, the larger aromatic rings shift the conformational equilibrium towards the more desirable sp conformer⁸⁹ (**Figure 23**).

2.3.3.1. Analysis of β -chiral primary alcohols

This improvement is especially significant in the analysis of chiral primary alcohols. In this case, only 9-AMAA provides sufficient differentiation which allows reliable structural assignment of the absolute configuration.^{69,71} The difference between 9-AMAA, MPA and MTPA is depicted in **Figure 26**.

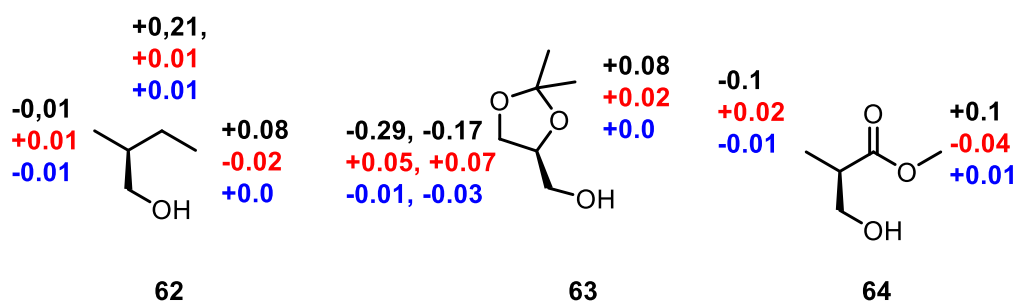


Figure 26 Comparison of $\Delta\delta^{\text{RS}}$ differences between 9-AMAA, MPA, MTPA esters

The $\Delta\delta^{\text{RS}}$ of 9-AMMA in derivatives **62**, **63**, and **64** are significantly larger than those obtained with the use of MPA or MTPA. It was concluded that MTPA or MPA are not suitable for the analysis of this type of alcohols and only 9-AMAA can be used. The conformation model is based on the previous models for MTPA and MPA and is shown in **Figure 27**.

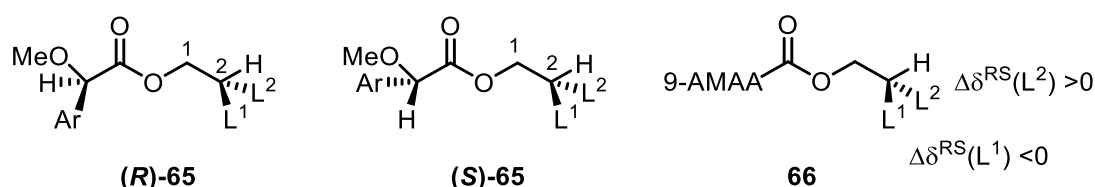


Figure 27 Conformational model for the configuration assignment of primary alcohols

The methoxy and carbonyl groups and the proton at the chiral center (C2) are in *syn*-periplanar conformation as shown in (*R*)-**65** and (*S*)-**65** (**Figure 27**). The aromatic moiety can produce a shielding effect towards the one of the substituents L^1 or L^2 . The analysis is then conducted in a similar manner

as with MTPA or MPA. The analysis of chiral primary alcohols and similar substrates is significantly more complex compared to the analysis of chiral secondary alcohols:

- The additional bond increases a flexibility of the whole system and increase the number of possible conformers.
- The chiral atom is located further from the functional group where the CDA is tethered.
- The substituents L^1 and L^2 are also located further from the anisotropic group which causes the differences in the chemical shift

Those effects combined cause the observed $\Delta\delta^{RS}$ values being significantly smaller compared to α -chiral secondary alcohols. The analysis can be further complicated by the presence of polar groups connected to the chiral center or by the lack of the observable signals in the substituents as can be exemplified with compounds **67**, **68**, and **69** (**Figure 28**). Apart from **69**, those compounds possess substituents on a chiral center without any protons attached (except for the proton itself, *vide infra*) therefore providing only one data point for analysis. This is not fully true for compound **69**, however the hydroxyl group proton is often exchanged with deuterium during the NMR experiment making them “invisible” in the experiment.

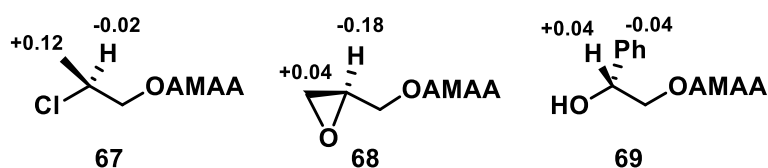


Figure 28 The examples of alcohols lacking protons at one of their substituents and their $\Delta\delta^{RS}$ values

This problem led to a development of new conformational model for cases like this, which utilizes the proton bonded to the chiral atom (**Figures 28, 29**). Previous models assumed this proton be coplanar (**Figure 27**) and therefore not showing any $\Delta\delta^{RS}$. This is frequently not true in real experiments, however the $\Delta\delta^{RS}$ is often smaller than those of substituents L^1 or L^2 . Similar behavior can be observed if bulky group, such as *Boc*, is present in the molecule. (**Figure 29**).⁹²

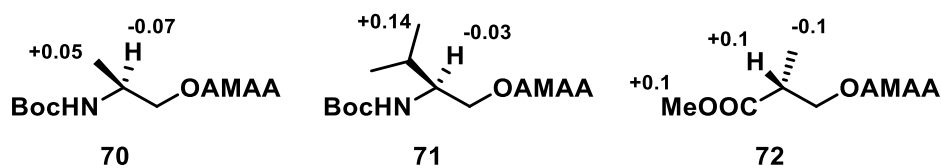


Figure 29 Major conformation of 9-AMAA esters with bulky substituents and observed $\Delta\delta^{RS}$

As can be seen in **Figures 28** and **29**, the bulky group is located coplanar to the carbonyl group of 9-AMAA and the proton and other substituent assume the non-coplanar position. Their chemical shifts are then analyzed in an analogous manner as described previously. The coplanarity of the bulky group is not exact and in some cases is slightly bent out of the plane. This non-planarity can be observed as $\Delta\delta^{RS}$ of the bulky group G (**72**, **Figure 29**). The modified model is presented in **Figure 30**.⁹²

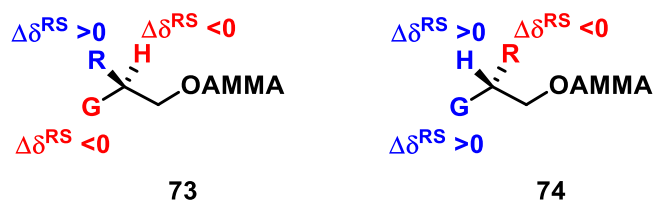


Figure 30 Conformational model for the assignment of the configuration of 9-AMAA esters of alcohols without protons in their substituents

2.3.3.2 Analysis of cyanohydrins

MPA can be used to analyze aldehyde⁷⁷ and ketone⁷⁸ cyanohydrins respectively. Although the cyanohydrin structure might structurally resemble secondary and tertiary alcohols, the presence of highly polar cyanide group strongly affects the conformation. Both ¹H and ¹³C spectra need to be analyzed, because the cyanide functional group possess no observable hydrogen atoms. Since the aldehyde cyanohydrins are a type of secondary alcohols, the conformation model described for the compounds with no observable protons present (**Figure 30**) cannot be used. The modified MPA-model is shown in **Figure 31**.

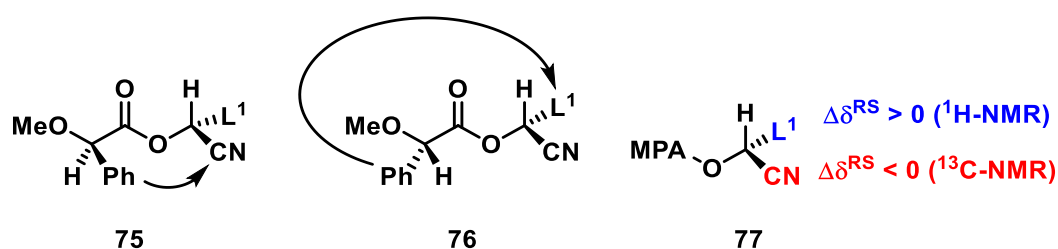


Figure 31 Conformational model for the assignment of the configuration of aldehyde cyanohydrins

The model (**Figure 31**) is based on the MPA model for an analysis of secondary alcohols (**Figures 22, 23**). Proton, carbonyl, and the methoxy group are in *syn*-periplanar conformation which allows the phenyl ring to project the anisotropic shielding effect towards one of the substituents, either cyanide group in (*R*)-MPA ester **75** or L¹ in (*S*)-MPA ester **76**. The chemical shifts are compared and $\Delta\delta^{RS}$ calculated as usual. In this case, also the ¹³C spectrum is used to calculate $\Delta\delta^{RS}(\text{CN})$ to obtain the

second data point for the analysis. If the configuration of the cyanohydrin is as shown in **77** in Figure 31, then the cyanide group has $\Delta\delta^{RS} < 0$ while the other substituent L^1 has $\Delta\delta^{RS} > 0$. Analogously, if the configuration is opposite, then the cyanide group has $\Delta\delta^{RS} > 0$ and the L^1 $\Delta\delta^{RS} < 0$.⁷⁷

The analysis of ketone cyanohydrins is more complicated since the esters are in a dynamic equilibrium.⁷⁸ Furthermore, the most stable conformer depends on the used enantiomer of MPA (**Figure 32**).

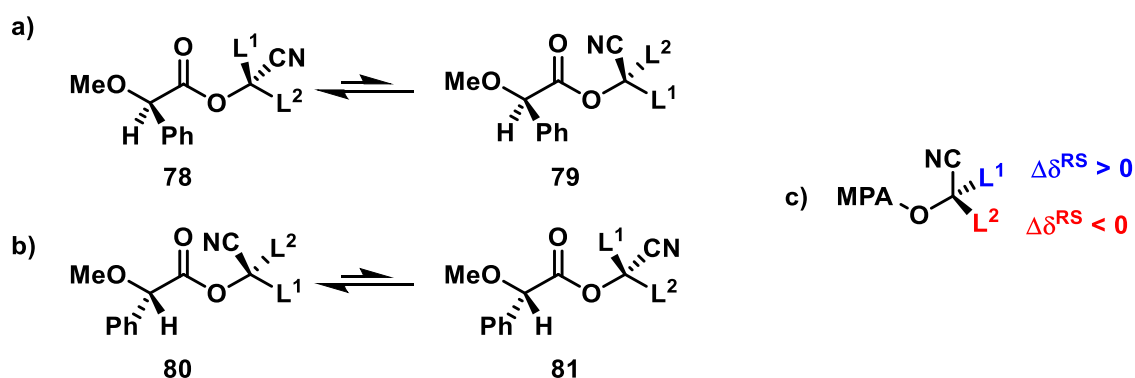


Figure 32 Conformational model for the assignment of the configuration of ketone cyanohydrins

a) Conformation of (*R*)-MPA esters b) Conformation of (*S*)-MPA esters c) simplification of the model

In the case of (*R*)-MPA esters (**Figure 32a**) conformer **78** is more stable than the conformer **79** by 2.84 kcal/mol. In the case of (*S*)-MPA ester (**Figure 32b**), conformer **80** (similar in spatial orientation of substituents as **79**) is more stable than **81** by 0.94 kcal/mol.⁷⁸ In both cases, the more stable conformers **78** and **80** have the cyanide group opposite to phenyl of the MPA. This dynamic equilibrium can be simplified in the model depicted in Figure 32c. The cyanide group is *syn*-periplanar with carbonyl and methoxy groups which puts the L^1 and L^2 into the shielding zone of the phenyl ring.

2.3.3.3. Analysis of tertiary alcohols

Although the ketone cyanohydrins structurally resemble tertiary alcohols, the analysis of tertiary alcohols is significantly underdeveloped. The main limitation is the difficulty of the esterification of such alcohols. The esterification is often low yielding, even though new and improved methods are emerging.⁹³ Furthermore, the substrate scope is limited to methyl substituted tertiary alcohols.^{74,75,94}

Both MTPA **56** and MPA **58** can be used in these cases. Both provide smaller $\Delta\delta^{RS}$ compared to 2-NMA **60** (**Figure 33**).^{74,75} As can be seen for compounds **83-85**, the $\Delta\delta^{RS}$ is in all cases smaller compared to the secondary alcohols and comparable to MPA and MTPA esters of β -chiral primary alcohols. In all cases the carbon in α -position to the chiral center showed anomalous value. Therefore, those are suggested to be excluded from the analysis. Furthermore, the list of the substrates tested was very limited and only included those bearing methyl groups as the third substituent on the chiral center. This

limitation is further increased because most of the tertiary alcohols tested were derived from geraniol. The probable cause is the lack of easily available enantiopure tertiary alcohols which could be used for the analysis.

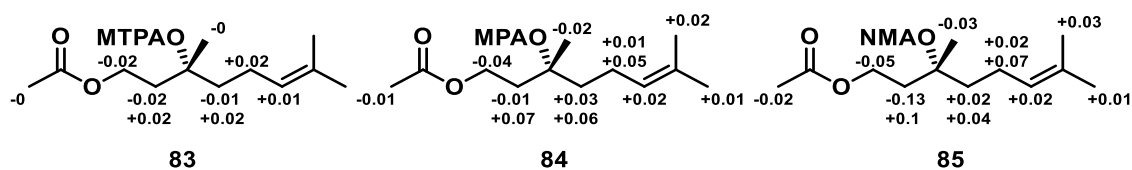


Figure 33 Examples of analyzed tertiary alcohols and $\Delta\delta^{RS}$ of their CDA esters

The conformational model is built upon the models previously developed for analysis of cyanohydrins and secondary alcohols by MTPA or MPA. Like previous models, the methoxy group, carbonyl and methyl groups are in *syn*-periplanar conformation. This leads to the projection of the shielding effect towards substituents L^1 or L^2 (**86**, **87** respectively, **Figure 34**). Due to the anomalous $\Delta\delta^{RS}$ observed for the α -position, proton and carbon signals associated with this position are omitted from the analysis as is shown in simplified model **88** (**Figure 34**).

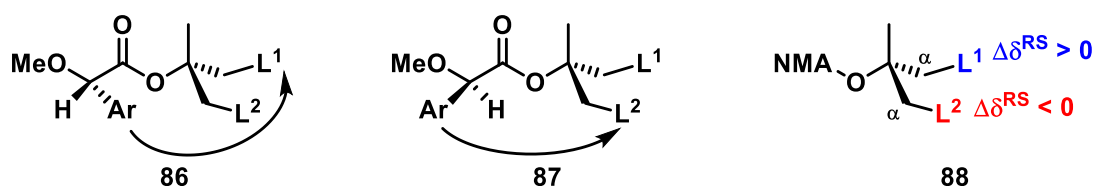


Figure 34 Conformation model for the assignment of the configuration of tertiary alcohols

2.3.4. Analysis of amines

2.3.4.1. Methoxyphenylacetic acid

The analysis of amines follows similar general procedures as analysis of hydroxy compounds. The most used CDA is MPA. MTPA can be used as well. The use of different arylacetic acids has not shown any significant improvement. The developed model for MPA is shown in **Figure 35**.⁹⁵ Compared to MPA esters (**Figure 22**), the conformational equilibrium mainly consists of the *ap* conformer which has the methoxy group *anti*-periplanar to the carbonyl group and the proton bonded to chiral center (**Figure 35a/b**). It is important to mention this conformational preference because application of the conformation model developed for MPA esters will lead to the opposite configuration when used with MPA amides. This simplified model for MPA amides is shown in **Figure 35c/d**.

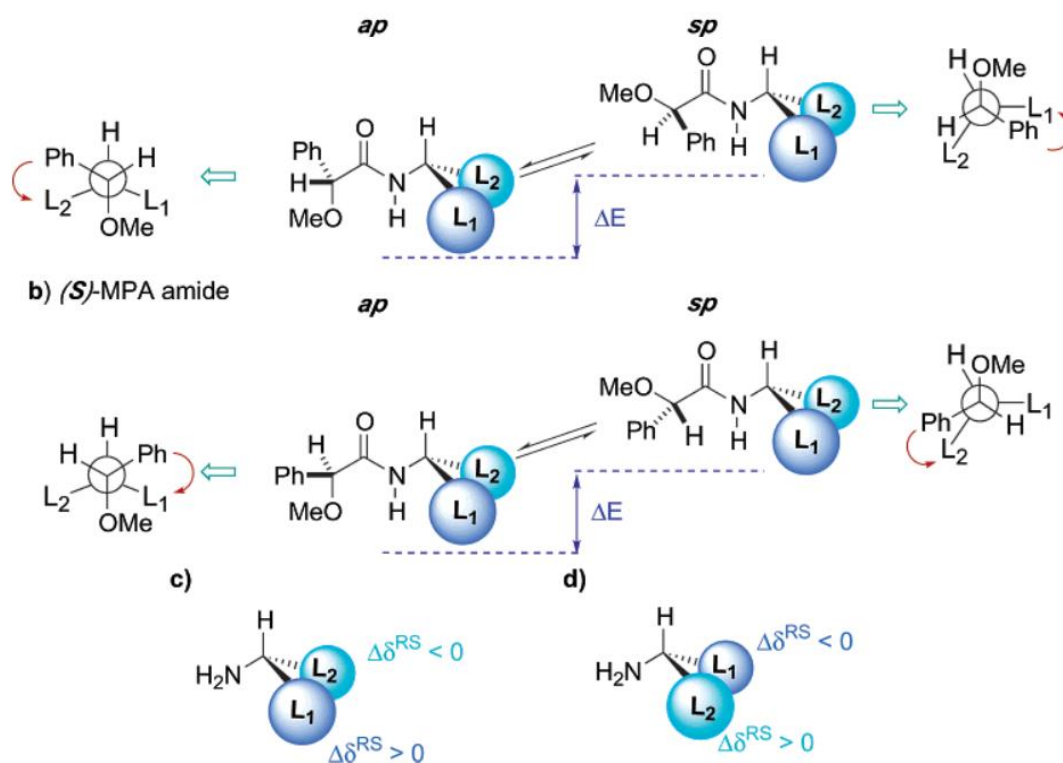


Figure 35 Major conformers of MPA amides (taken from ref.⁸⁵)

2.3.4.2. Boc-phenylglycine

Boc-phenylglycine was tested as a CDA for analysis of amines because unlike in case of esters, the structural modification of the phenylacetic acid based CDAs did not have any significant effect. Compared to MPA or MTPA, Boc-phenylglycine possess several advantages over arylacetic acids:⁷⁰

- Like MPA, the conformational equilibrium consists of only two conformers, but the phenyl group is better positioned compared to MPA
- Like MTPA the phenyl ring is in the better position but the effect of this ideal positioning in the case of MTPA is diluted by higher number of conformers.

The most NMR relevant conformer is shown in **Figure 36**. In the NMR-relevant *ap* conformer the proton on the phenylglycine moiety is in the *anti*-periplanar conformation with the carbonyl group and the proton on the chiral center. This configuration allows selective projections of the shielding effect towards the substituents. The calculations of $\Delta\delta^{RS}$ and configuration assignment are conducted analogously to the previously described MPA esters or amides.

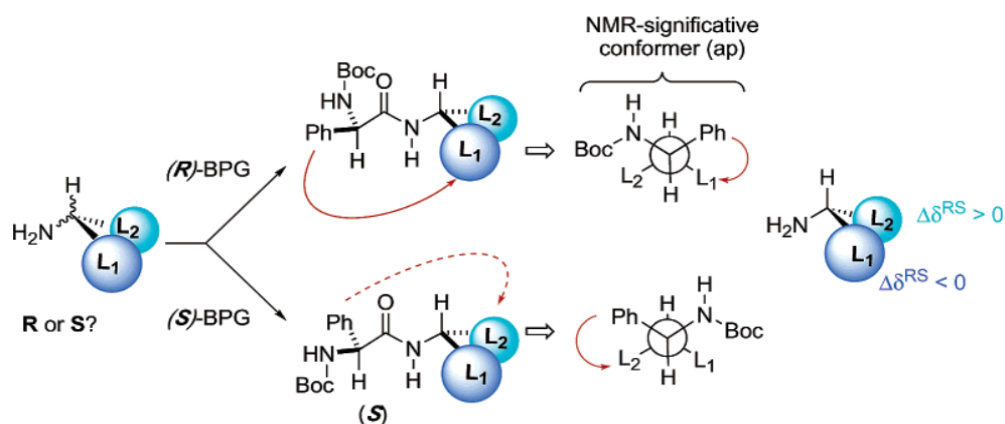


Figure 36 Conformational model for the configuration assignment of chiral amines using boc-PHG (taken from ref.⁸⁵)

2.3.5. Analysis of polyfunctional compounds

The analysis of polyfunctional compounds could be also performed and was thoroughly reviewed by Seco.⁹⁶ It can be divided into two categories:

- The case where the multiple bonded CDA does not interfere and therefore the analysis can be conducted in the same manner as described before.
- The case where the multiple bonded CDAs interfere and therefore new models need to be described for the analysis of such compounds.

The examples of case a) are shown in **Figure 37**. In both *ent*-pimarane⁹⁷ **89** and foliasalacioside E1⁹⁸ **90** MTPA esters, the CDAs are bonded far apart from each other and show no interference between them. Previously described models can be used in the analysis of such compounds.

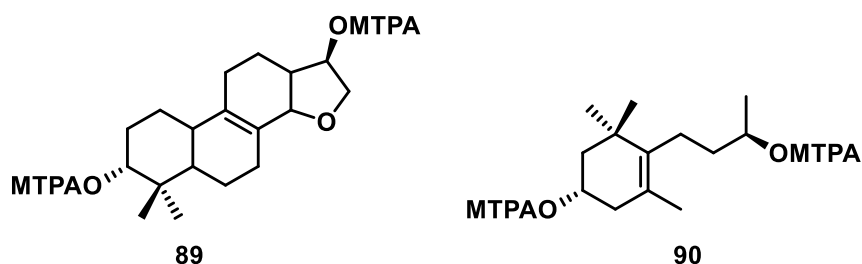


Figure 37 Configuration assignment of polyfunctional terpenes

In the case where the CDAs are located closer together, the interference of their influence towards the substituents in the molecule is complex and therefore new conformational models were developed. The models developed for 1,2, 1,3 and 1,4-diols are shown in **Figure 38**. In those cases, the diols are

esterified with 2 equivalents of CDA to yield (*R,R*)-diester and (*S,S*)-diester and their NMR spectra are compared in similar manner as described previously.⁹⁶

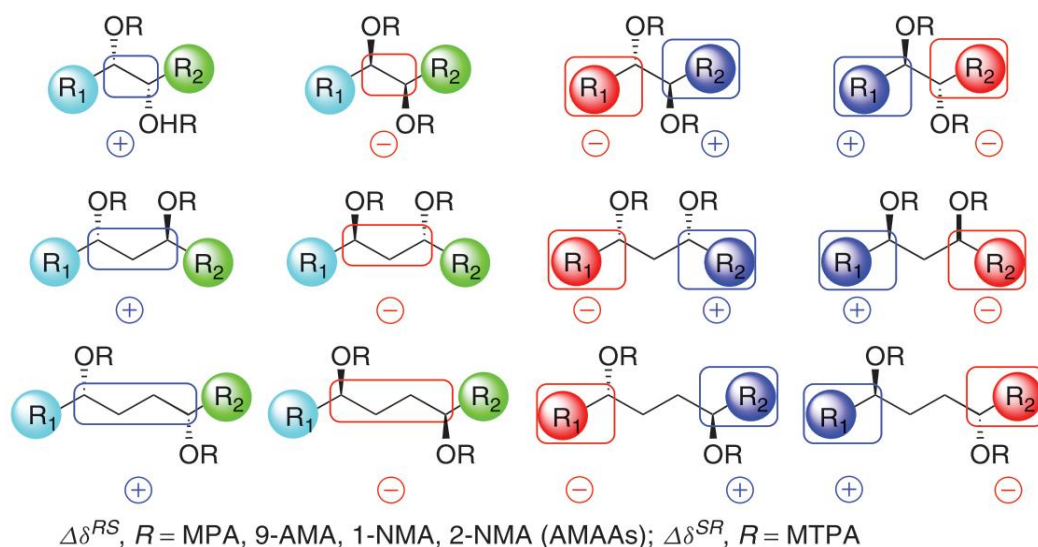


Figure 38 Observed differences of polyfunctional compounds with overlapping CDA effects (taken from ref.⁹⁹)

The analysis of 1,2-amino alcohols proceeds similarly to 1,2-diols. Different behavior is observed compared to diols and different conformational model is required (**Figure 39**).

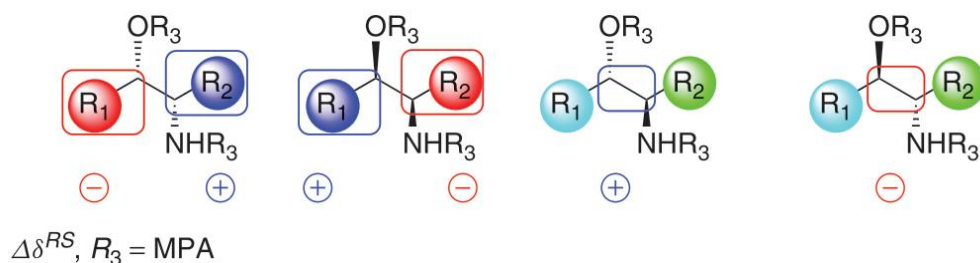


Figure 39 Observed differences of polyfunctional compounds with overlapping CDA effects (taken from ref.⁹⁹)

The modification of previously described methods was recently reported by Orlov.¹⁰⁰ The modification consists of performing the derivatization in the NMR tube without any purification. By using DCC/DMAP acylation in CDCl_3 , the precipitated urea byproduct rises to the top of the solvent or falls to the bottom of the NMR tube based on the used solvent (**Figure 40**).

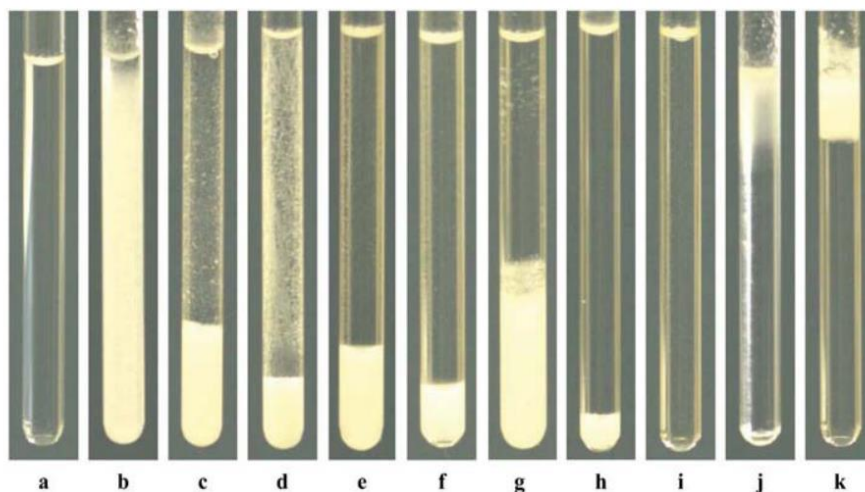


Figure 40 a) mixture of CDA and analyte, b) after addition of DCC, DMAP and shaking for 2 mins reactions after 1 hour in various deuterated solvents: c) ACN d) acetone e) toluene f) benzene g) THF h) DMF i) DMSO j) CS₂/DCM 4:1 k) CDCl₃ Picture taken from ref.¹⁰⁰

The common NMR probe (**Figure 41a**) allows measurements of such samples because the measurement area is located approximately in the middle of the NMR tube as shown in **Figure 41b/c**.

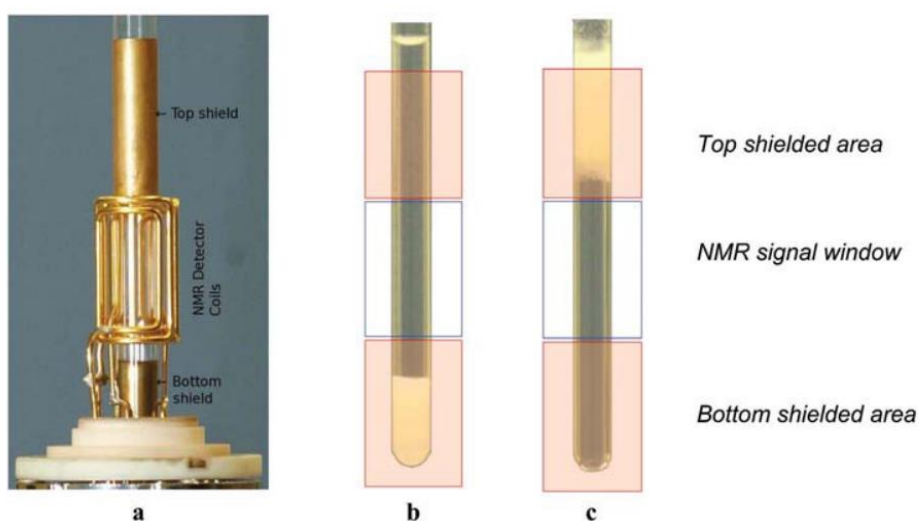


Figure 41 a) Common NMR probe b) schematics of NMR signal window and location of the residual resin. (Taken from ref.¹⁰⁰)

This method allows quick routine NMR configuration assignment or enantiomeric purity measurement of simpler structures. However, the presence of unreacted material might complicate more complex 2D NMR experiments.

Similar modification was already reported by Seco who used resin-bound MPA¹⁰¹ for the analysis. Further addition of a scavenger resin traps any unreacted DMAP and MPA leaving only the MPA ester present in a solution. The procedure was further modified using the mixed resin containing (*S*)- and (*R*)-

MPA in the 2:1 ratio. This allowed immediate configuration assignment because the mixture contained uneven ratio of diastereomers as can be seen in **Figure 42**. MTPA and boc-phenylglycine resins were explored as well but they lost their floating properties which made them unsuitable.

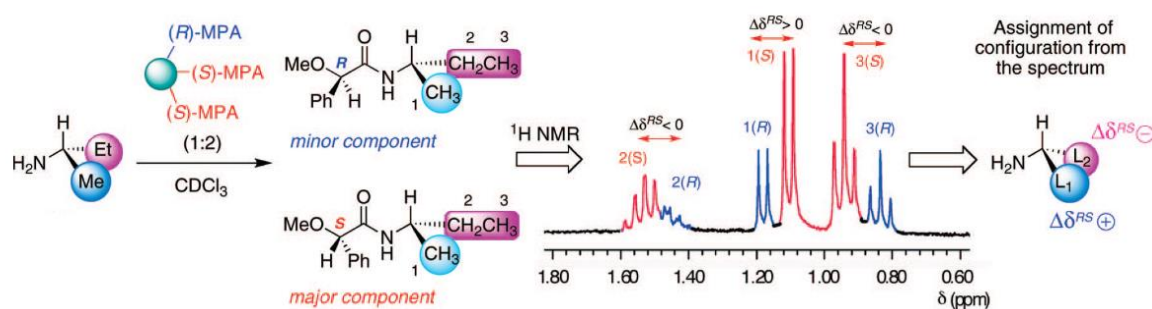
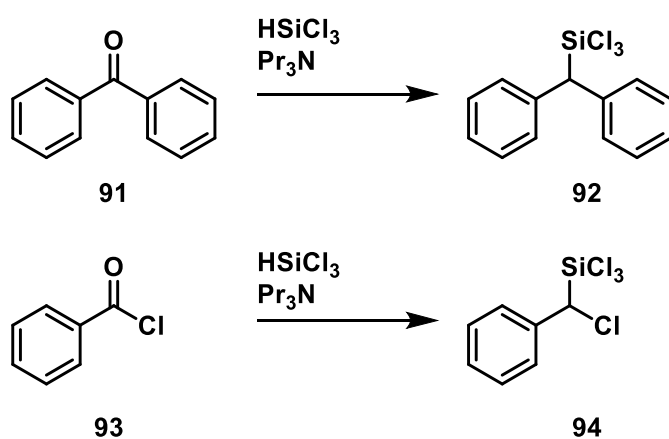


Figure 42 Assignment of the absolute configuration using resin bound CDA (taken from ref.¹⁰¹)

2.4. Organocatalytic HSiCl_3 reduction of ketimines

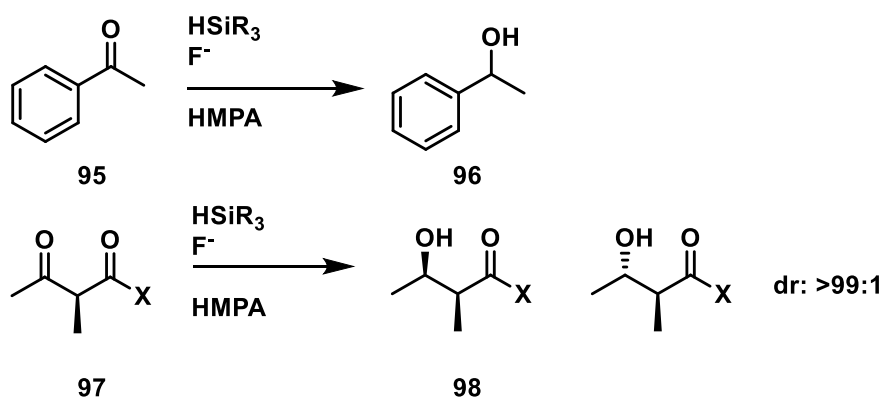
The reduction of prochiral ketones or ketimines leading to chiral alcohols or amines is one of the most important chemical transformations. There are various methods available; some of them used in pharmaceutical industry were reviewed.^{102,103} Those reaction often require use of metal catalysts which, although used in low % loadings, are not environmentally friendly.^{104,105} The organocatalytic reductions provide interesting alternative because they do not require the use of transition metals. There are several approaches available: transfer hydrogenation using Hantzsch ester or other hydrogen sources and chiral acids, frustrated Lewis pairs and hydrogen gas, borane reduction with CBS catalyst or trichlorosilane reduction using chiral catalysts.^{106,107} Allylation reaction using allyl-trichlorosilanes were reviewed by Denmark.¹⁰⁸ Due to the focus of the last project of this thesis on trichlorosilane reductions, only this area will be reviewed.

One of the first examples of using trichlorosilane as a reducing agent comes from Benkeser (**Scheme 14**).¹⁰⁹



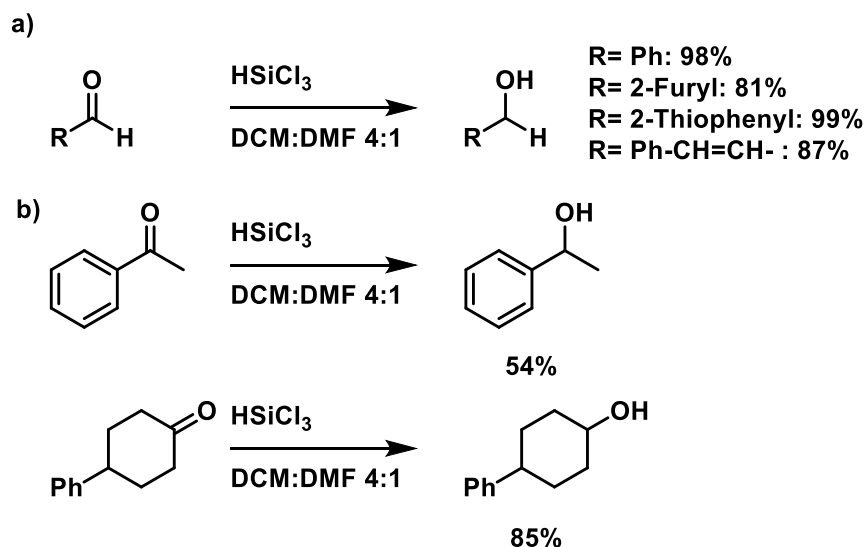
Scheme 14 First examples of reduction using HSiCl_3

Although organosilicon compounds were isolated instead of alcohols, it provided an interesting approach towards the organosilicon compounds from carbonyls. The first real reduction of aldehydes and ketones was described in 1988 by Fujita who used fluoride source to activate the silane (Scheme 15).¹¹⁰ The product **96** was obtained after the hydrolysis of the resulting silyl-protected alcohols. Furthermore, the reaction proceeded with high *threo*-selectivity in the case of reduction of α -substituted- β -keto esters or amides **97** \rightarrow **98**. Unfortunately, toxic HMPA as a solvent was required.



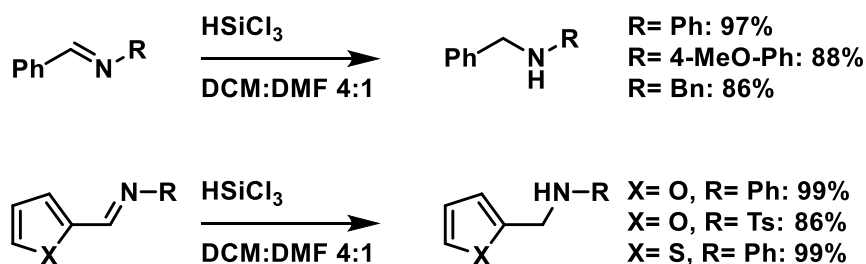
Scheme 15 Fluorine catalyzed reduction of ketones

Further modifications were performed by Kobayashi.¹¹¹ DMF was used to form active hypervalent silicon species which is the active reducing agent in the reaction. As could be seen in Scheme 16a the reaction proceeded with high yields using aldehydes as starting materials. Reduction of ketones proceeded slower with lower yields (**Scheme 16b**).



Scheme 16 DMF catalyzed reduction of ketones

High yields, although slightly lower compared to aldehydes, were also obtained for a reduction of aldimines (**Scheme 17**). The *In-situ* reduction was also possible with yields ranging from 75 – 93 %. This further expanded the scope to imines which are difficult to isolate.



Scheme 17 DMF catalyzed reduction of imines

This methodology was further expanded to the chiral DMF (**Figure 43**) equivalent **99** to promote an organocatalytic asymmetric addition of allylsilanes (**Scheme 18**).¹¹²

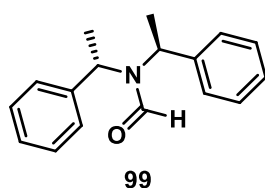
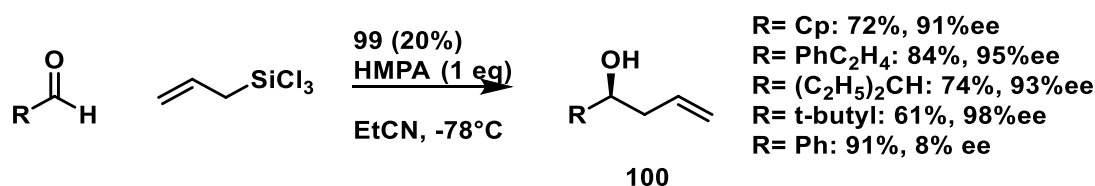
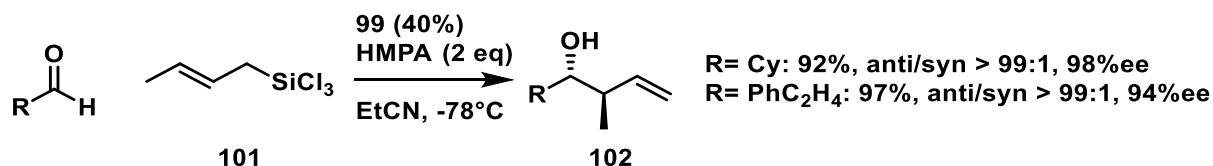


Figure 43 Chiral DMF analogue



Scheme 18 Enantioselective allylation of aldehydes

One equivalent of HMPA was used and various homoallylic alcohols were prepared in high yields (61 – 91 %) and excellent enantioselectivity (91 - 98 %). In the case of the benzaldehyde allylation only 8% enantiomeric excess was observed. This methodology was further expanded on crotylation using (E)-crotylsilane **101** to obtain homoallylic alcohols **102** with high enantioselectivity and diastereoselectivity (**Scheme 19**).



Scheme 19 Enantioselective crotylation of aldehydes

Another reported ligands for asymmetric allylation come from Denmark who developed chiral phosphoramidites to obtain allylated products in high yields (67 – 95 %) and moderate enantioselectivity (21 - 60 %ee).¹¹³

Asymmetric reductions with silanes in a combination with transition metal catalysts are well known.^{114–116} The first organocatalytic asymmetric hydrosilylation of ketone imines comes from Iwasaki who developed chiral formamides based on proline.¹¹⁷ Whole sets of ligands **103-104** were prepared and tested (**Figure 45**). The formamide moiety was proved to be essential for reactivity: reductions were attempted with DMAc as an activator, but no product was obtained.

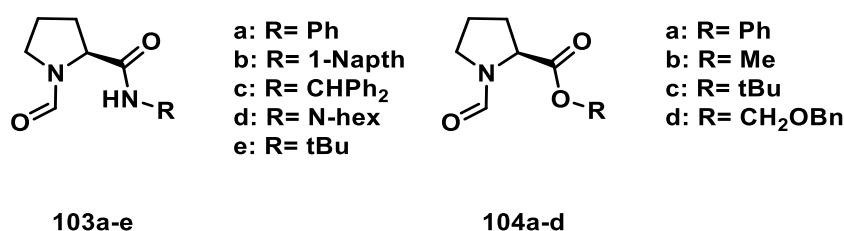
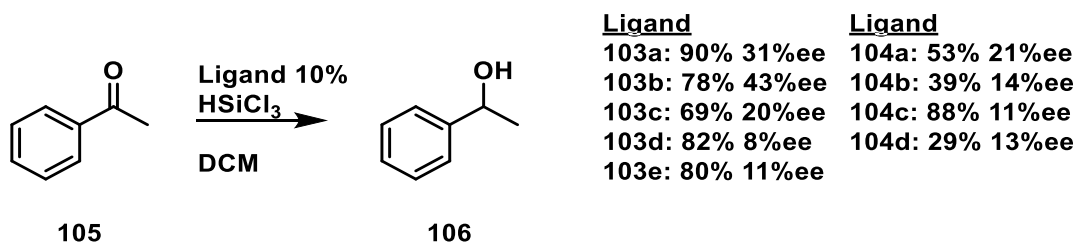


Figure 45 Proline-based formamide catalyst

The ligands were first tested to reduce acetophenone **105** (**Scheme 20**). The resulting phenylethanol **106** was obtained in high yields and moderate enantiomeric excess in the case of ligands **103**. Ligands **104** with an ester functionality provided products in lower yields and low enantiomeric excess.



Scheme 20 Enantioselective reduction of ketones by proline-based catalyst

Five more ketones were reduced with ligands **103a** and **103b** and the alcohols were obtained in lower yields 21 – 87 % and similar enantioselectivity (8 – 51 %).

Ligands **103a** and **103b** were further used as ligands for asymmetric reduction of imines which were isolated in high yields (55 - 98 %) and moderate enantioselectivity (49 - 66 %ee).¹¹⁸ Based on the (*R*)-configuration of the major enantiomer the transition state (**Figure 46**) was proposed. Trichlorosilane is activated by the coordination of the ligand and the partially positively charged silicon atom is further coordinated by the imine nitrogen. The reduction is furnished by the hydride transfer *via* the 4-membered

cyclic state. The orientation of the imine shown in **Figure 46a**. The transition state leading to product with (*S*)-configuration is disfavored due to the steric interaction between aromatic rings (**Figure 46b**).

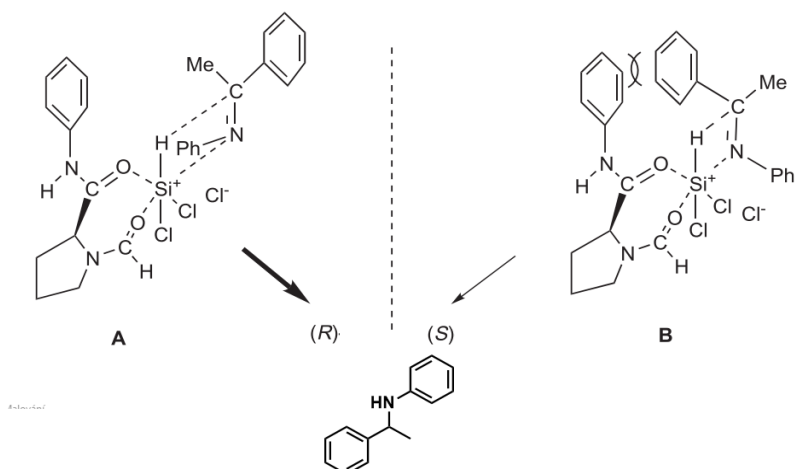


Figure 46 Transition state for the reduction of imines by **103a**. Taken from ref.¹¹⁸

Kočovský further independently developed a similar valine based ligand **107**.¹¹⁹ Multiple valine-based ligands were prepared with the optimal structure shown in **Figure 47**.

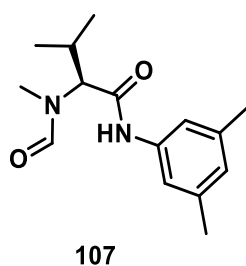
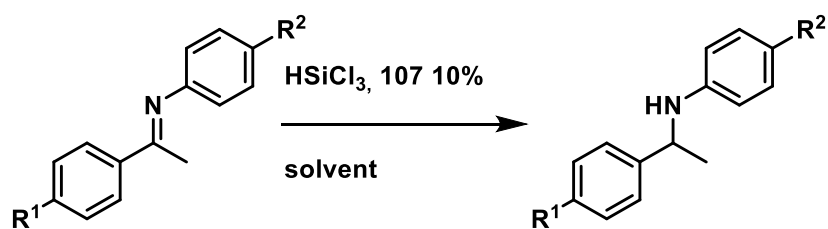


Figure 47 Valine-based ligand by Kočovský

The ligand was evaluated on variety of substituted imines (**Figure 48**). The products were isolated in high yields (70 – 95 %) and enantioselectivities (87 - 92 % ee). The yields were slightly higher when the reaction was conducted at lower temperature -20 °C (entries 1,4,6 vs entries 2,5,7) The effect of the low temperature on stereoselectivity was minor. The change of a solvent from CHCl₃ to toluene proved to be beneficial: the enantioselectivity of the reaction conducted in toluene at RT matched those attempts conducted in CHCl₃ at lower temperatures: entries 8,10,11 vs. 2,5,7.



Entry	R ¹ / R ²	Solvent	Yield	%ee	Temperature
1	Ph / Ph	CHCl ₃	70	89	RT
2	Ph / Ph	CHCl ₃	94	92	-20°C
3	4-MeOPh / Ph	CHCl ₃	62	87	RT
4	4-CF ₃ Ph / Ph	CHCl ₃	88	87	RT
5	4-CF ₃ Ph / Ph	CHCl ₃	95	89	-20°C
6	Ph / 4-MeOPh	CHCl ₃	79	86	RT
7	Ph / 4-MeOPh	CHCl ₃	85	90	-20°C
8	Ph / Ph	Toluene	81	92	RT
9	4-MeOPh / Ph	Toluene	86	85	RT
10	4-CF ₃ Ph / Ph	Toluene	86	89	RT
11	Ph / 4-MeOPh	Toluene	85	91	RT
12	2-MePh / Ph	Toluene	90	92	RT

Figure 48 Reduction of prochiral imines catalyzed by **107**

Although the ligand **107** had the same configuration as previously reported proline ligands **103** products with the opposite configuration were isolated. The transition state was proposed based on the configuration of the products (**Figure 49**).

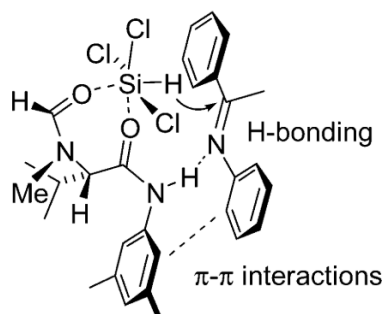


Figure 49 Transition state proposed for the reduction catalyzed by ligand **107**, taken from ref.¹¹⁹

Trichlorosilane is activated by a coordination of formyl and amide carbonyl oxygens forming the active species. The imine is further activated by the hydrogen bond from the amide nitrogen and the whole complex is held together by $\pi - \pi$ interactions between the phenyl ring of the imine and the catalyst. Interestingly, this aryl-aryl interaction was reported to be the key for the high enantioselectivity in spite of the previously reported transition state for proline-based ligands **103** (Figure 46).¹¹⁷ This phenomenon was investigated further with the sets of modified ligands.¹²⁰ ¹³C NMR confirmed the coordination of both formamide and amide oxygen atoms to HSiCl₃. The methyls in the amide moiety become non-equivalent suggesting a hindered rotation around the C-N bond. Based on this investigation, the key features of the catalytic system were proposed (Figure 50).

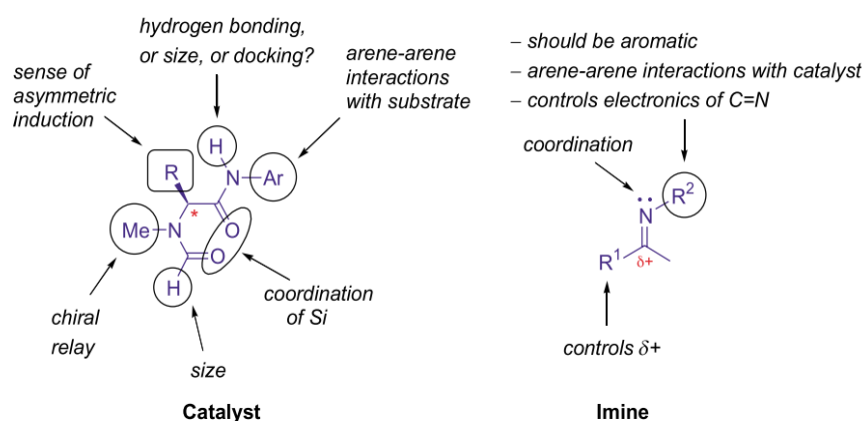


Figure 50 SAR of the amino acid-based catalysts. Taken from ref¹²⁰

The structure of the ligand was further modified by increasing the steric bulk of the structure yielding ligand **108**¹²¹ (Figure 51), which is commercially available. Ligand **108** was tested on more than 60 imines¹²² with various structures including heteroaromatic and aliphatic imines. The yields were high: 20 – 99 %, mostly 60 – 99 % and enantioselectivities as well 6 – 95 % mostly 75 – 95 %. The low yields and enantioselectivities were encountered in the case of some heteroaromatic imines, especially pyridine-based which could coordinate to HSiCl₃ and induce the reaction *via* achiral transition state. This was confirmed by an increase of the steric bulk around the pyridine nitrogen atom using 2,6-diisopropyl substitution which increased the enantioselectivity from 21 to 78 %ee compared to the unsubstituted pyridine derivative. 2-chloroacetophenone derived imines were reduced as well. Further treatment with the base yielded chiral aziridine derivatives with high enantiomeric purity.¹²¹

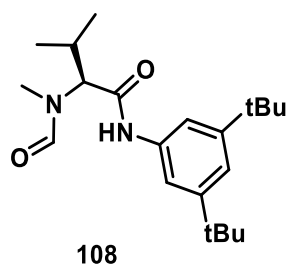


Figure 51 Optimized structure of valine-based catalyst

The structure was further modified and included a fluororous tag¹²³ which simplified the separation of the ligand. The ligand was also immobilized to an insoluble polymer carrier¹²⁴ which allowed the catalyst to be reused at least five times without the loss of the activity.

Structurally different oxazoline-pyridine ligands were also reported by Kočovský¹²⁵ (**Figure 52**)

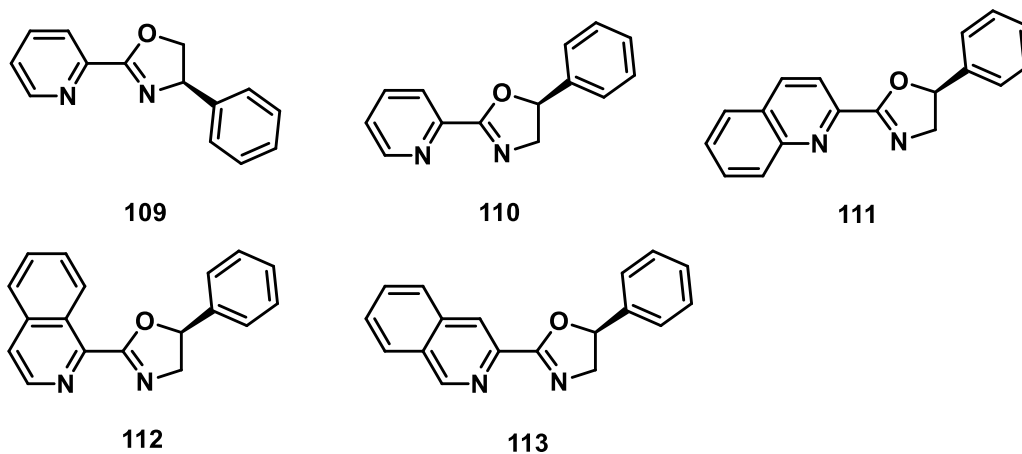


Figure 52 Oxazoline-based ligands

At first acetophenone was used as a model ketone. Ligand **109** derived from phenylglycinol provided products in low 29% yield and 66% ee. This was significantly lower compared to previously described ligands. The isomeric ligand **110** derived from the mandelic acid provided enantioenriched alcohol in 85% yield and 78% ee which was comparable to previously reported ligands. Lower reactivity of the ligand **109** is caused by the close presence of the phenyl ring which is hindering the approach of the substrate as can be seen in the intermediate **114**. This effect is not noticeable in the assumed intermediate **115** derived from the ligand **110** as can be seen in **Figure 52**. For this reason, further ligand optimization was conducted using the mandelate based structures **111-113**.¹²⁵

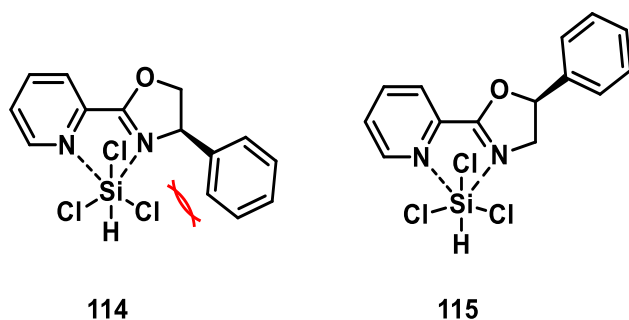


Figure 52 Proposed differences in transition states in reduction of imines with ligands **109** and **110**.

The best ligand showed to be **111** which provided reduced ketones in high yields 50 – 85 % and enantioselectivities 70 - 95 %ee. In the case of ligand **110**, no products were isolated. Reduction of aliphatic ketone, cyclohexyl methyl ketone provided product in 70% yield but as a racemate. This suggests that $\pi - \pi$ interactions might play a role as in the case of the ligand **107** (**Figure 49**). The proposed transition state is shown in **Figure 53**.¹²⁵

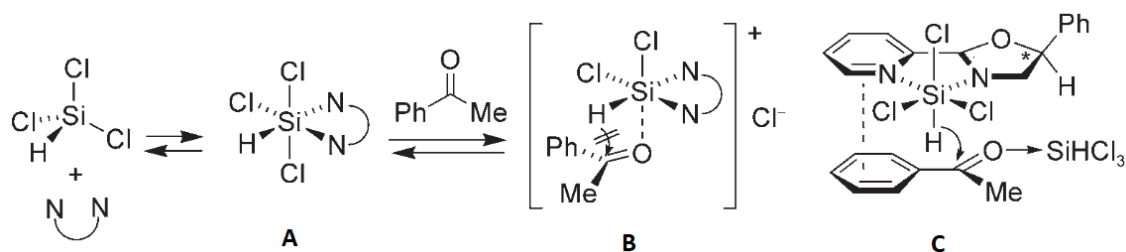


Figure 53 Proposed transition state for the HSiCl_3 reduction with ligand **107**. Taken from ref.¹²⁵

At first the ligand coordinates to HSiCl_3 forming hexacoordinated silicone intermediate (**Figure 53a**). The intermediate can then react via 4-membered transition state (like one depicted on **Figure 46**) after the carbonyl oxygen coordinates to the silicon atom by displacing one of the chlorine ligands (**Figure 53b**). This transition state was deemed unlikely due to the high strain in the 4-membered ring. Therefore the proposed transition state (**Figure 53c**) included the activation of the ketone via the coordination to another HSiCl_3 molecule while interacting with the ligand via aryl-aryl interaction.¹²⁵

Pyridine-based ligands were developed by Zhang. The optimal structure **116** is shown in **Figure 54**.¹²⁶

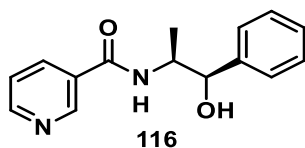
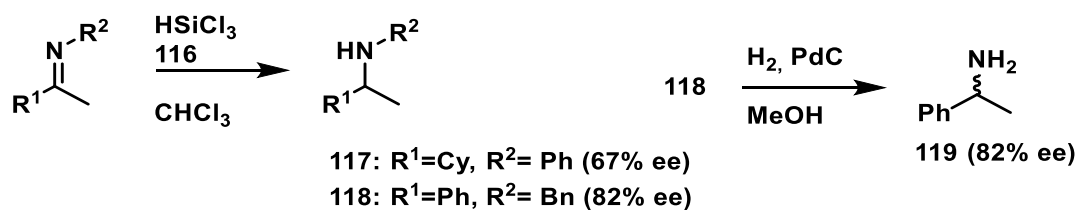


Figure 54 Zhang's pyridine ligand

Ligand **116** catalyzed the reduction of various imines in high yields (80 – 95 %) and enantioselectivity (61 – 95 %). This included imine **117** derived from aliphatic ketone and benzylamine-derived imine **118** which after deprotection yielded amine **119** (Scheme 21).



Scheme 21 Reduction of imines with ligand **116**

Different picolinic acid derived ligands were reported by Celentano^{127,128} based on the binaphthyl-2,2'-diamine including *N*-oxide **121** (Figure 55). Ligand **120** provided amines in quantitative yields and moderate enantioselectivity (73 – 82 %). The *N*-oxide derivative **121** yielded products in low yields 40 – 75 % and inferior enantioselectivity (< 40 %ee).

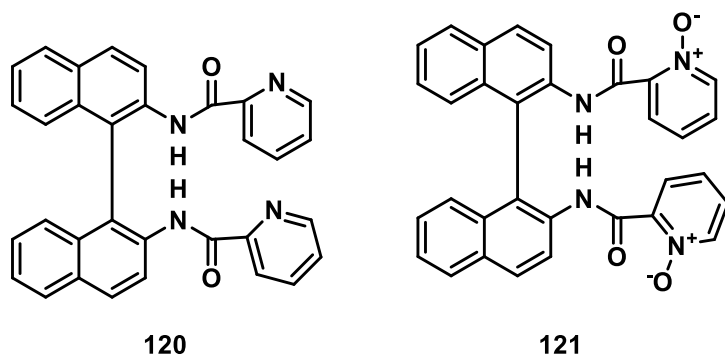


Figure 55 BINAM-derived ligands

Recently, chiral sulfinamide catalyst **122** (Figure 56) was reported¹²⁹ and yielded amines in good yields (45 – 90 %) and enantioselectivity (>90 %ee). (*P*)-chiral phosphine oxide ligand **123** and derivatives were presented by Jones.¹³⁰ Only low enantioselectivity was observed (< 40 %ee, mostly around 20 %).

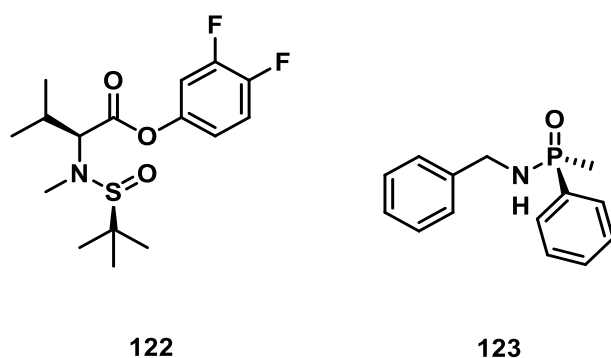


Figure 56 *S* and *P*-chiral ligands

3. Discussion and results: Project NMR

3.1. Synthesis of 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoic acid

3.1.1. Introduction

The structure of 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoic acid (TBBA) **1** is shown in Figure 1. The main features include the CF₃ group which should allow easy configuration assignment based on ¹⁹F NMR. The carboxylic group functions as a tether to connect the analyte *via* an ester or amide bond. Last, the shielding effect is produced by the benzimidazole ring towards one of the substituents of the analyte. The main advantage over other CDAs is the lower flexibility of the mostly aromatic system which possesses fewer flexible bonds compared to arylmethoxyacetic acids.

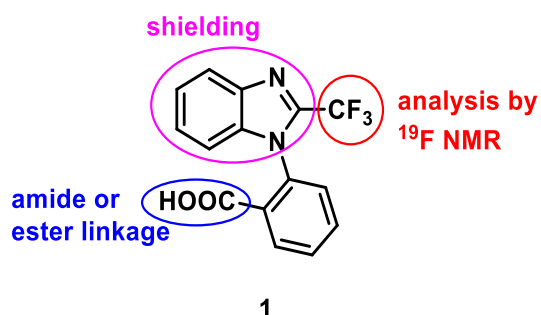
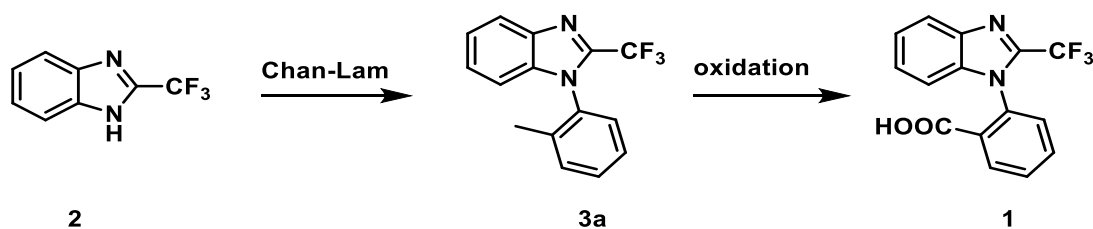


Figure 1 Structure of 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoic acid (TBBA) **1**

The proposed synthesis is depicted in **Scheme 1**. The key step is Chan-Lam arylation of the benzimidazole **2** with 2-tolylboronic acid¹³¹, followed by the oxidation by KMnO₄ to yield **1** with subsequent chiral resolution of the racemate.



Scheme 1 Proposed Chan-Lam based synthesis of **1**

3.1.2. Chan-Lam approach

The starting benzimidazole **2** was prepared by refluxing *o*-phenylenediamine in trifluoroacetic acid according to the literature procedure in the high yield.¹³² The reported arylation conditions were tried with *o*-tolylboronic acid (*o*-tolylBA, **Table 1**, entries 1 and 2). No product was observed on TLC or HPLC analysis. To check the viability of the reaction conditions, less sterically hindered *p*-tolylboronic acid was used as a model substrate (entries 3, 4) and the catalyst loading was increased as well. Following those promising experiments with *p*-tolylboronic acids, further copper catalysts were screened with *o*-tolylboronic acid as a substrate (entries 5-11). Only traces of the product were observed in HPLC analysis. The use of 2-boronobenzoic acid (entries 12, 13) yielded no product. The low reactivity was caused by the unfavorable structures of reagents: sterically hindered electron poor benzimidazole and sterically hindered boronic acid make this coupling challenging. Because it was envisioned that the resolution of **1** by a crystallization is going to require higher amounts of racemic material (gram scale), the coupling approach was abandoned.

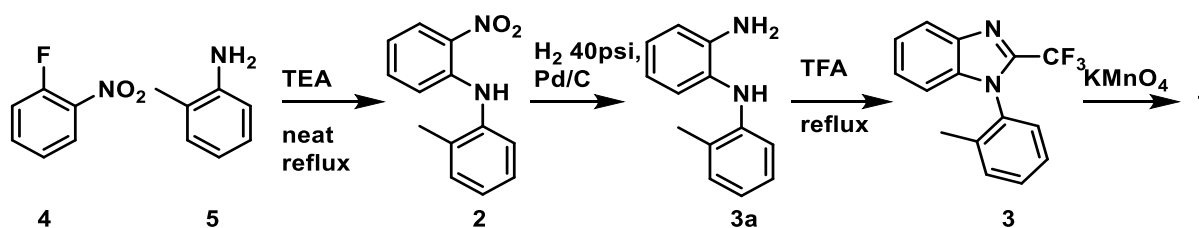
Table 1 Chan-Lam coupling to **3a**

Entry	Catalyst, %mol. equivalents	Base	Boronic acid	Solvent	Result
1 ¹³¹	Cu ₂ S, 25%	TMEDA 1eq	<i>o</i> -tolylBA 1.5eq	DMF	No reaction
2 ¹³³	Cu(NO ₃) ₂ , 20%	TMEDA 10%	<i>o</i> -tolylBA, 2eq	MeOH	No reaction
3	Cu ₂ S, 50%	TMEDA 1eq	<i>p</i> -tolylBA 1 eq	DMF	70%*
4	Cu(NO ₃) ₂ , 100%	TMEDA 2eq	<i>p</i> -tolylBA, 2 eq	MeOH	45%*
5	Cu(OAc) ₂ ·H ₂ O, 100%	Pyridine 2eq	<i>o</i> -tolylBA, 2eq	DMF	Traces*
6	CuO, 100%	Pyridine 2eq	<i>o</i> -tolylBA, 2eq	DMF	No reaction
7	CuBr, 100%	Pyridine 2eq	<i>o</i> -tolylBA, 2eq	DMF	Traces*
8	CuI, 100%	Pyridine 2eq	<i>o</i> -tolylBA, 2eq	DMF	Traces*
9	Cu(BF ₄) ₂ , 100%	Pyridine 2eq	<i>o</i> -tolylBA, 2eq	DMF	Traces*
10	Cu(NO ₃) ₂ , 100%	Pyridine 2eq	<i>o</i> -tolylBA, 2eq	DMF	Traces*
11	Cu ₂ O, 100%	Pyridine 2eq	<i>o</i> -tolylBA, 2eq	DMF	No reaction
12	Cu ₂ S, 25%	TMEDA, 4eq	<i>o</i> -COOH-PhBA, 2eq	DMF	No reaction
13	Cu(OAc) ₂ , 100%	Pyridine 2eq	<i>o</i> -COOH-PhBA, 2eq	DMF	No reaction

* Percentage of total area of peaks in HPLC at 260 nm

3.1.3. Cyclization approach

An alternative arylation-cyclization approach was investigated. At first the 2-fluoronitrobenzene **4** was arylated with *o*-toluidine **5** followed by the reduction of the nitro group and subsequent cyclization¹³² to yield benzimidazole **3**.



Scheme 2 Synthesis of **1** by oxidation of **3a**

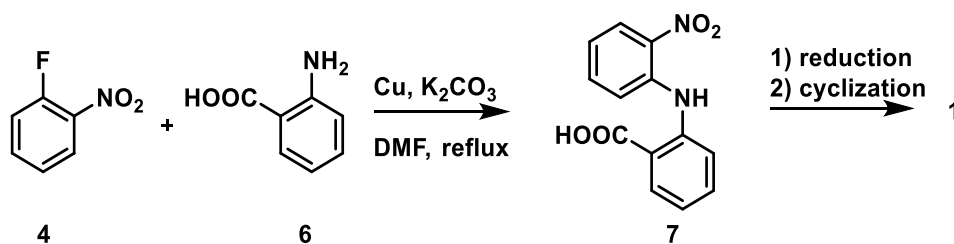
Multiple arylation conditions were tried with mixed results. The results are summarized in **Table 2**. The product was obtained in 70% yield when NaH was used as a base. The use of triethylamine without any solvent provided product in 60% yield after simple dilution with water and filtration of the product. No product was observed when the reaction was performed in water (entry 3) or neat with DBU as a base (entry 4).

Table 2 *N*-arylation of 2-methylaniline **5** with 2-fluoronitrobenzene **4**

Entry	Eq. 5	Base	Solvent	Temperature	Yield
1 ¹³⁴	0.7	NaH	DMF	RT	70%
2	1	Et ₃ N	neat	150°C	60%
3 ¹³⁵	1	--	water	100°C	No reaction
4 ¹³⁶	1	DBU	neat	80→130°C	No reaction

The reduction of the nitro group was performed by catalytic hydrogenation with palladium on carbon (Pd/C) as a catalyst at 40 PSI. Traces (<5% by HPLC) of starting material were still observed in the reaction mixture. Purification by column chromatography was performed and the product was isolated in 75% yield. The arylated diamine **3** was then cyclized in boiling TFA and isolated after the extraction in 50% yield. Subsequently, the oxidation was carried out with KMnO₄ in the water. However, due to a poor solubility of the starting material the reaction was sluggish and proceeded very slowly (60% conversion after 48 hours at reflux). The poor solubility was not the only problem. The product was isolated in a form of oil and, therefore, it adhered to the side of the reaction vessel, which further reduced the surface area available for the reaction. No product was isolated; however, an alternative approach was developed in parallel.

Further literature screening revealed another possible route which does not include the sluggish methyl oxidation step at the final stage of the synthesis. At first, 2-fluoronitrobenzene **4** was arylated with anthranilic acid **6**, followed by the reduction of the nitro acid **7** and the ring closure. This approach (**Scheme 3**) prevented not only the problematic oxidation step, but also the arylation. Moreover, the reduction steps were reported on large scale.¹³⁷



Scheme 3 Proposed synthesis of TBBA

The synthesis started with copper catalyzed Ullmann arylation. Compound **7** was isolated after a recrystallization from acetic acid in 70% yield. The reaction worked on multiple scales ranging from 700 mg to 33 g and was reproduced multiple times on the large scale with the yields between 70 – 80 %. The yield tent to increase with the reaction scale due to the slight difficulties in a work-up. The following reduction was slightly modified. Instead of Raney nickel and hydrogen at high pressures, Pd/C and a balloon filled with hydrogen at atmospheric pressure was used. Using 5 mol% of palladium catalyst, the reaction was complete within two hours. The high speed of the reaction allowed the reduction of the catalyst amount. In the end, 1 mol% of catalyst was used, and the reaction was finalized after 16 hours (overnight). Simple filtration through a short pad of silica or celite and subsequent evaporation provided the product in almost quantitative yields. The reaction was scaled up to 22 g of starting material. Further scale up was not possible due to the lack of suitable glassware: the solubility of nitro acid **7** in ethyl acetate is relatively low and the reaction starts in a suspension. Furthermore, if the reaction flask was more than half filled with the reaction mixture, the rate of the reaction decreased. This was likely caused by the reduction of the surface contact between the reaction mixture and hydrogen gas in the flask.

The final cyclization was more complex than expected. Using the previously described conditions (refluxing TFA) yielded a complex mixture of products; however, desired benzimidazole **1** was detected in HPLC in approximately 30 %. Multiple other products were detected, and their plausible structures deduced from the LC-MS analyses are depicted in **Figure 2**.

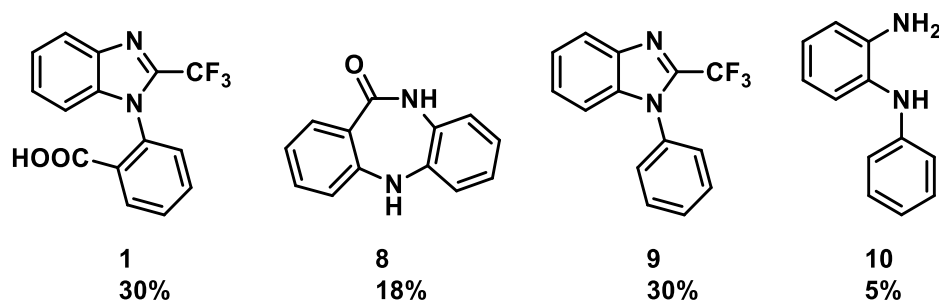


Figure 2 Proposed structures of byproducts after cyclization to **1**

Unsurprisingly, the 1,4-dibenzodiazepine was also detected. Interestingly, the decarboxylated compounds **9** and **10** were detected in the HPLC-MS analysis as well. Although unexpected, the

examples of acid catalyzed decarboxylation can be found in the literature.^{138,139} Optimization of the cyclization reaction is shown in **Table 3**.

Table 3 Cyclization to TBBA

Entry	Reagent	Solvent	Temperature	Result
1	TFA	Neat	70°C	30%*, complex mixture
2	TFA	Neat	50°C	No reaction
3	TFA	Neat	RT	No reaction
4	TFA	DCM	RT	No reaction
5	TFAA	neat	RT	mixture
6	TFAA 10eq	THF	RT	mixture
7	TFAA 10eq	dioxane	RT	mixture
8	TFAA 10eq	acetone	RT	mixture
9	TFAA 10eq	CHCl ₃	RT	mixture
10	TFAA	neat	40°C	40-95% isolated yield
11	TFAA 3eq	toluene	90°C	60% isolated yield

* Percentage of total area of peaks in HPLC after integration at 260 nm

At first, milder conditions were attempted. The reduction of the reaction temperature provided no product. Further dilution with DCM did not provide any improvements as well. The use of more reactive trifluoroacetic anhydride (TFAA) showed significant improvement. The use of various solvents (entries 6-9) gave a mixture of products. The cyclization in the boiling neat TFAA provided a complete conversion to the product which was isolated in 40% yield after extractive work-up. Further optimization of the work-up improved the yields to 95% after simple precipitation in cold water. Slow addition into a large excess of cold water and vigorous stirring was found to be crucial. Higher rates of addition or slow stirring produced a gray-green oily material which was difficult to filter and contained residues of TFAA and TFA locked inside the solid material. Luckily, this material can be dissolved in a minimal amount of MeOH and re-precipitated again. Slow addition during vigorous stirring yielded light gray solid powder. The reaction was further scaled up to yield 15 g of **1** after precipitating in 2.7 liters of cold water under stirring with an overhead stirrer. Use of 3 equivalents of TFAA in toluene provided the product as well, however a byproduct identified as a mixed anhydride of the product and TFA was observed. This anhydride was attempted to hydrolyze with sodium hydroxide and after extractive workup the product was isolated in 60% yield. In the end of the optimization, the reaction in neat TFAA was used to produce racemic **1** on 15 g scale multiple times with high reproducibility.

3.2. Resolution of enantiomers

3.2.1. Crystallization

The resolution via crystallization was challenging. TBBA has good solubility in all tested organic solvents (EtOAc, THF, EtOH, acetonitrile, acetone, acetic acid and methanol) and usually precipitates by the addition of water. The results are summarized in **Table 4**. The use of MeOH, isopropanol, acetonitrile, or THF as a solvent did not lead to precipitated product. The addition of the resolving agent in water instantly yielded oily compound with no enantiomeric enrichment. The low solubility of the resolving agent and TBBA was attempted to overcome by a use of hydrochloride salt of the resolving agent and sodium salt of TBBA both being soluble in water. The mixing of their aqueous solutions immediately produced an oily precipitate, which was not soluble in water even after heating; however, no enantiomeric enrichment was observed.

Table 4: Resolution of TBBA by crystallization

Resolving agent	Eq.	Solvent	Additive	Results
(<i>R</i>)-1-phenylethan-1-amine	1	MeOH		No crystallization
(<i>R</i>)-1-phenylethan-1-amine	1	Water		oil
(<i>R</i>)-1-phenylethan-1-amine	1	Isopropanol		No crystallization
(<i>R</i>)-1-phenylethan-1-amine	1	Acetonitrile		No crystallization
(<i>R</i>)-1-phenylethan-1-amine	1	THF		No crystallization
(<i>R</i>)-1-phenylethan-1-amine.HCl	1	Water (0.15M)	KOH	No crystallization
(<i>R</i>)-1-phenylethan-1-amine.HCl	0.5	Water (0.15M)	KOH	No crystallization
(<i>R</i>)-1-phenylethan-1-amine.HCl	0.5	Water (0.1M)	KOH	No crystallization
(<i>R</i>)-1-phenylethan-1-amine.HCl	1	Water (0.3M)	KOH	oil
(<i>R</i>)-1-phenylethan-1-amine.HCl	0.5	toluene		No crystallization
PE-I-mix* ¹⁴⁰	1	MeOH		No crystallization
PE-I-mix* ¹⁴⁰	1	Acetonitrile		No crystallization
PE-I-mix* ¹⁴⁰	1	EtOAc		No crystallization
(<i>L</i>)-Proline	1	MeOH		No crystallization
Quinine	1	MeOH		No crystallization
(<i>S</i>)-Phenylglycinol	1	MeOH		No crystallization

* PE-I-mix: equimolar mixture of (*R*)-1-(*p*-chlorophenyl)ethylamine, (*R*)-1-(*p*-bromophenyl)ethylamine, (*R*)-1-(*p*-methylphenyl)ethylamine.

The so called “Dutch resolution”^{140–142} method was tried based on the experience from chiral resolution in one of the other projects. In general, the “Dutch resolution” is a method which utilizes a

mixture of resolving agents used at once. Not only it allows rapid screening of various resolving agents, but often the components of a resolving mixture do not yield resolved material when used by themselves instead of in a mixture. It was shown that the diastereomeric salts consists of unequal ratios of the resolving agents and the minor component play important role in the crystallization.^{140,141} Nevertheless, even this modified method did not work. Further, a few more resolving agents were attempted with zero success.

3.2.2. Conversion to diastereomers

Since the resolution by crystallization did not work, other methods were explored. Acid **1** was converted into diastereomeric amides using L-alanine-methyl ester as a model example to develop suitable acylation conditions.

Table 5 Acylation of L-alanine methyl ester with TBBA

Entry	Reagent	Solvent	Results
1	T3P+pyridine	EtOAc	No reaction
2	Ethyl chloroformate	DCM	Complex mixture
3	CDI	THF	Complex mixture
4	SOCl ₂	Toluene, reflux	70% isolated yield
5	(COCl) ₂ , cat. DMF	Toluene	No reaction
6	EDCI, HOBt	DMF	65% isolated yield

Acylation conditions are summarized in **Table 5**. Use of propylphosphonic anhydride / pyridine in EtOAc (entry 1) provided no reaction.¹⁴³ Formation of mixed anhydride via ethyl chloroformate (entry 2) or CDI (carbonyldiimidazole) (entry 3) yielded complex mixtures of products. Following those reactions, we turned to two-step process via the intermediate acyl chloride (entry 4, 5). Five equivalents of SOCl₂ in toluene at reflux provided the acyl chloride in the quantitative yield while the use of oxalyl chloride-DMF at room temperatures proved to be unsuitable. The acyl chloride was then reacted with the amine in the presence of triethylamine as a base to provide amides **11-13** (**Figure 3**). The use of carbodiimide activator was explored as well (entry 6) with 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) in a combination with 3-hydroxybenzotriazole in DMF provided similar results to the use of thionyl chloride. Due to much faster reactivity, the acyl chloride method was preferred initially. The diastereomeric mixture was inseparable by common methods.

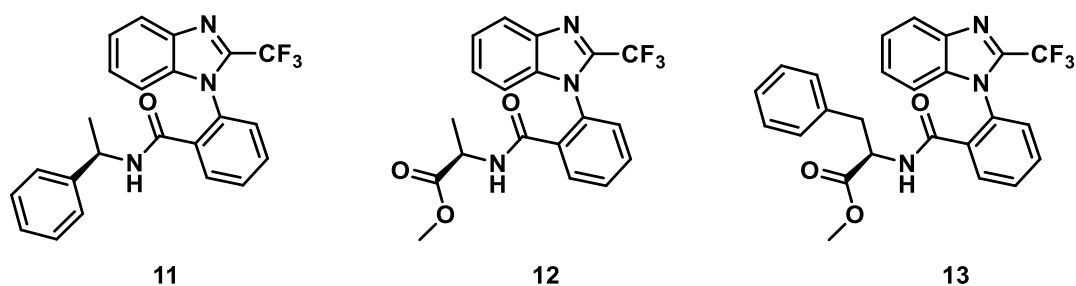


Figure 3 Amides prepared for separation of atropisomers

Different amides were formed (**Figure 3**): (*R*)-1-phenylethan-1-amine **11**, L-alanine-methyl ester **12**, and L-phenylalanine-methyl ester **13**. Amide **11** provided 100:3 dr. after three crystallizations from EtOAc: hexane mixture in a low yield (10%). Although the resolution via the synthesis of diastereomeric amides did not work, the analysis of the NMR spectrum of amide **11** revealed reasonable separation of the signals in NMR spectra (**Figure 4**), which would allow the configuration assignment if a suitable conformation model was developed.

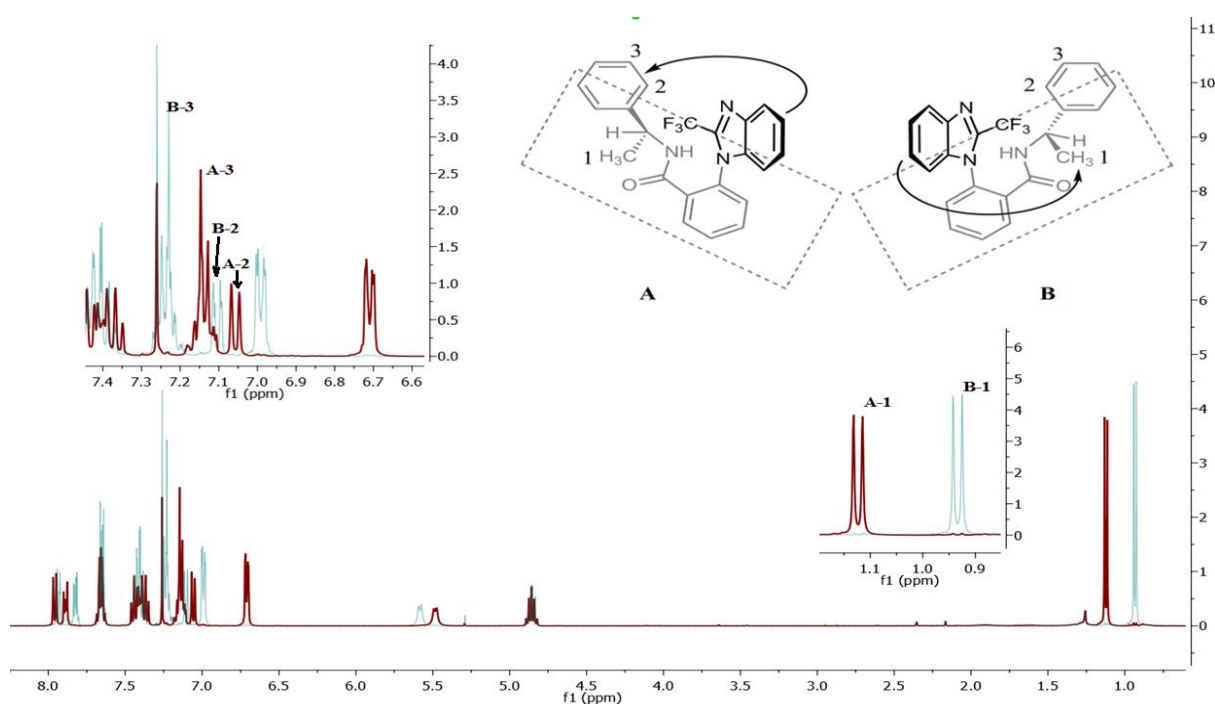
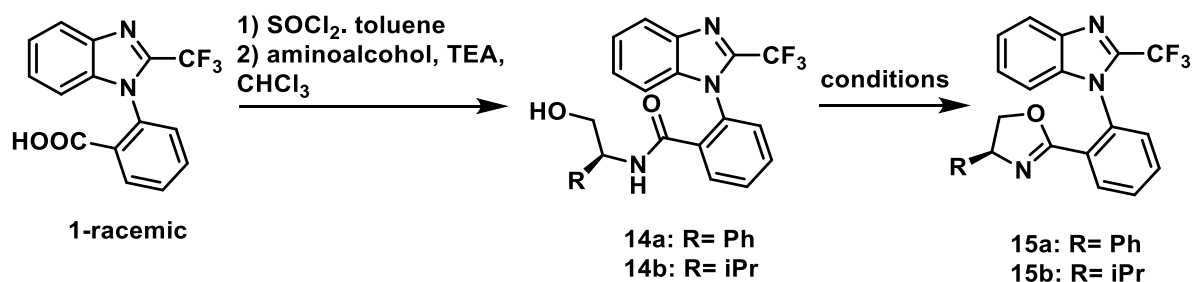


Figure 4 Overlapping NMR spectra of amide **11**

It was assumed the high flexibility of the amide is the cause of the difficult separation. More rigid oxazolines **15a** and **15b** were explored (**Scheme 4**). Multiple methods were investigated to form oxazolines.



Scheme 4 Two-step synthesis of oxazoline **15**

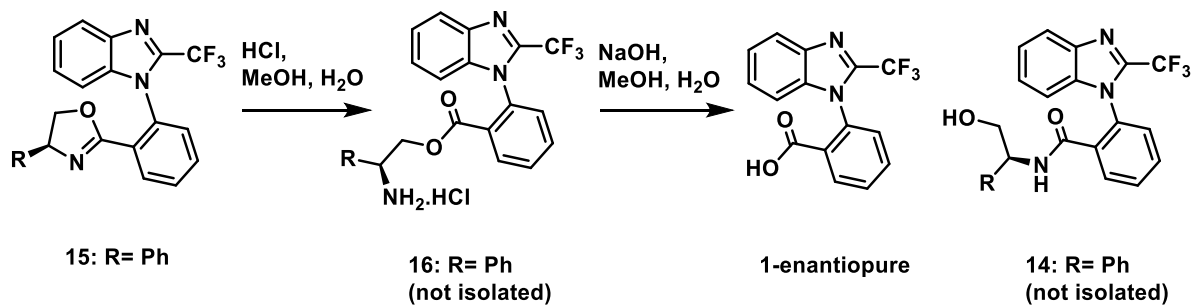
Direct conversion of **1** into **15** was attempted by heating of the acid in a presence of the amino alcohol in toluene. No product was observed. Next, amides **14a** and **14b** were prepared using the previously described method, but it was not possible to separate the diastereomers by chromatography. Various cyclization conditions were then explored (**Table 6**).

Table 6 Synthesis of oxazolines **15**

Entry	Conditions	Results
1 ¹⁴⁴	Direct reaction of 1 with amino alcohol	No reaction
2 ¹⁴⁵	BF ₃ .OEt	No reaction
3	T3P, TEA	Trace conversion ^a
4 ¹⁴⁶	MsCl, TEA, DMAP	50% conversion ^a
5 ¹⁴⁷	pTSA,	No reaction
6 ¹⁴⁸	SOCl ₂ then NaOH	60-80% isolated yield ^b

^a by HPLC ^b calculated for each respective diastereomer

The cyclization with BF₃.OEt (entry 2) yielded no product, while the use of propanephosphonic acid anhydride (T3P) shown traces of new products on TLC and HPLC. Most importantly, those spots were sufficiently separated to allow preparative separation (entry 3). The cyclization using MsCl and base provided approximately 50% conversion according to the HPLC analysis. The acid catalyzed dehydration (entry 5) did not show any product. Two step reaction with SOCl₂ and then aq. NaOH provided full conversion to oxazolines **15a** and **15b** which were then separated using common column chromatography with 60 and 80% yields for each diastereomer. The separation could not be scaled up above approximately 2g scale due to the poor separation of the diastereomers. This could be partially overcome by a separation of the mixed fractions by second column chromatography. Nevertheless, further scale up was not attempted.



Scheme 5 Hydrolysis of oxazolines **15**

The oxazoline was hydrolyzed using HCl promoted the ring opening followed by NaOH hydrolysis of the resulting ester **16** (Scheme 5). Byproduct **14** was observed during the hydrolysis.¹⁴⁹ Fortunately, it was possible to remove this byproduct by simple extraction and enantiopure acid **1** was isolated by a precipitation from water in 60 - 70% yield. The enantiomeric purity was confirmed by chiral SFC analysis as shown in **Figure 5**.

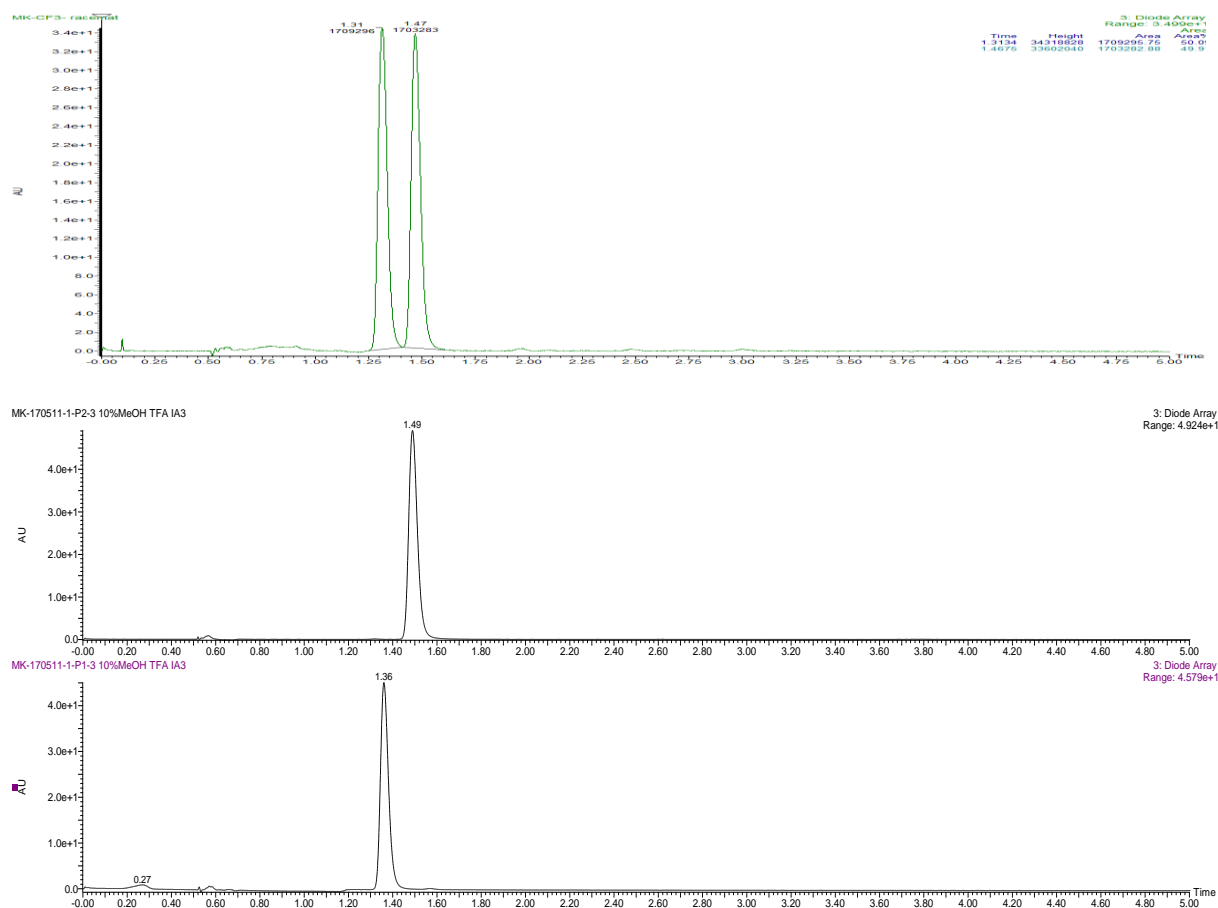


Figure 5 TOP: racemic mixture, MIDDLE: (*M*)-TBBA, BOTTOM: (*P*)-TBBA

The absolute configuration of the chiral axis was determined by the single crystal X-Ray crystallography of the derivative **11** prepared from the enantiopure TBBA (**Figure 6**).

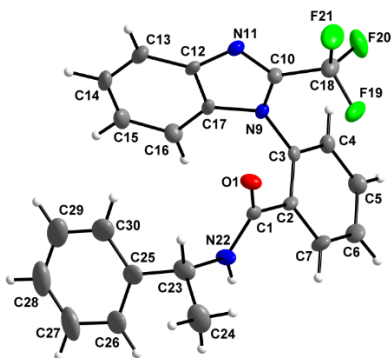
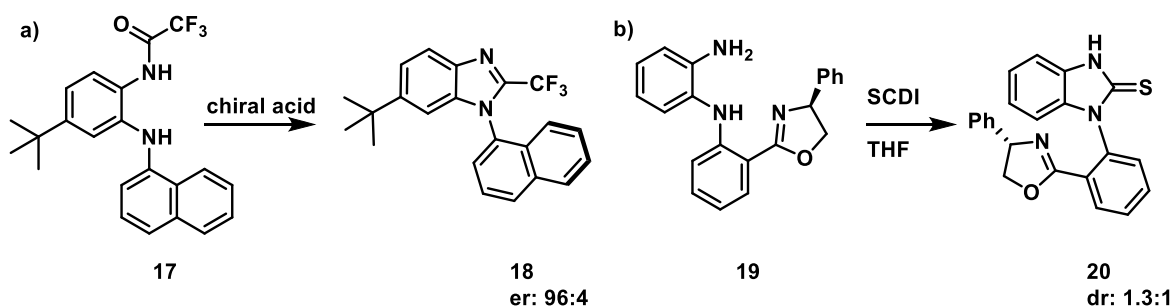


Figure 6 The molecular structure of (*R,P*)-**11** (CCDC 1871600) together with the atom labelling scheme. The thermal ellipsoids are drawn at the 50% probability level. Only one of the seven crystallographically independent molecules is depicted for clarity.

3.3. Atroposelective synthesis

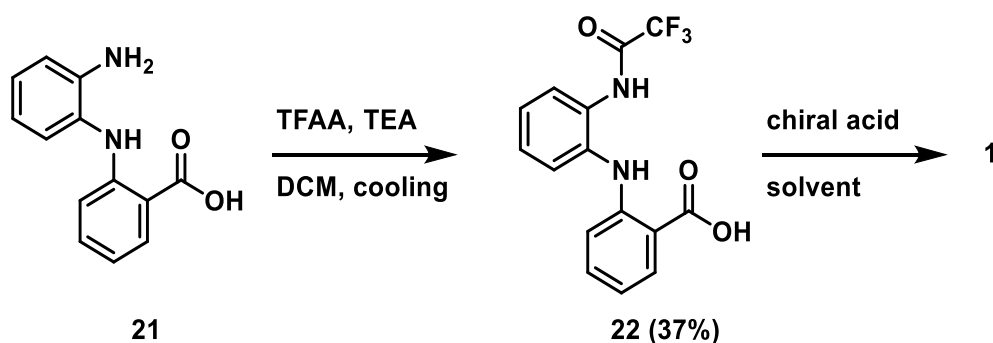
Recently, atroposelective approach to 2-trifluoromethylbenzimidazoles was published by Miller group (**Scheme 6a**). The chiral acid catalyzed cyclization of the trifluoroacetamide **17** yielded the benzimidazole derivative **18** in high enantiomeric excess.^{45,46} Similar approach towards the atroposelective synthesis was already attempted in our group by undergraduate student David Profous (**Scheme 6b**),¹⁵⁰ however, the results were disappointing. The cyclization of oxazoline **19** with various cyclization reagents yielded benzimidazoles, however the diastereomeric ratio was poor and the best result was obtained in the ratio 1.3:1 dr. for benzimidazole **20**.



Scheme 6 a) atroposelective cyclization by Miller^{45,46} b) atroposelective synthesis by David Profous¹⁵⁰

This led us to investigate the possibility of the atroposelective routes towards **1**. At first the starting materials had to be prepared. The acylation of the amino acid **21** to form trifluoroacetamide **22** seemed straightforward at first and the product was isolated by a simple filtration in 37% yield (**Scheme 7**).

Unfortunately, the reaction was close to be impossible to reproduce but enough material was isolated to attempt the atroposelective cyclodehydration.



Scheme 7 Proposed synthesis of **1** by atroposelective cyclization

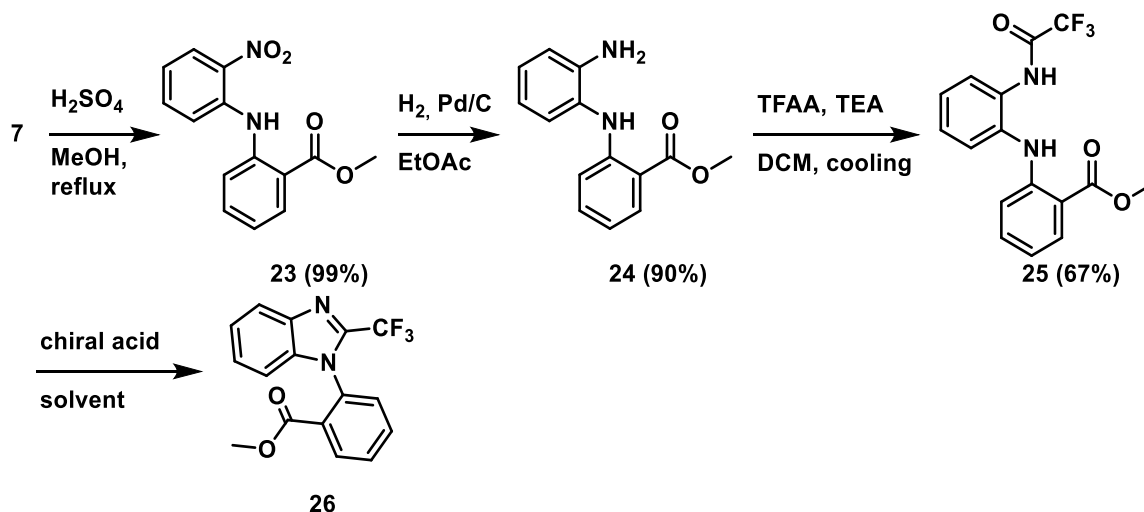
Various chiral acids were tested in the model reaction. The results are summarized in **Table 7**. Only trace conversion (<5%) was observed in entries 1-6. Nevertheless, the reaction mixtures were submitted to chiral SFC analysis, and the enantiomeric ratio was determined. At first, 10-camphorsulphonic acid (10-CSA) was tested (entry 1) which provided the acid in 25/75 enantiomeric ratio with the (*M*)-isomer being the major one. Tartaric acid derivatives (entries 2-4) showed similar enantioselectivity as 10-CSA. In the case of dibenzoyl L-tartaric acid (entry 2), small crystals appeared in the flask after standing at room temperature. The solid material was racemic while the filtrate shown similar enantiomeric ratio as 10-CSA. Both L-proline and (*R*)-Mandelic acid did not yield any improvements (entries 5 and 6). BINOL-derived phosphonic acid (*S*)-TRIP (entry 7) did not yield any product at all. Toluene was used as well to increase the reaction rate at higher temperature. However, TLC analysis after 24 hours showed only faint shadows of the product, which was not possible to analyze *via* chiral SFC (only the starting material was detected).

Table 7 Chiral acid catalyzed cyclization from **21** to **22**

Entry	Acid	Solvent	Er.
1	10-CSA	THF (65°C)	25 / 75
2	Dibenzoyl-L-tartaric acid	THF (65°C)	26 / 74 50 / 50 (precipitate)
3	Dianisoyl- L-tartaric acid	THF (65°C)	26 / 74
4	Ditoluoyl-L-tartaric acid	THF (65°C)	26 / 74
5	L-proline	THF (65°C)	40 / 60
6	(<i>R</i>)-Mandelic acid	THF (65°C)	28 / 72
7	(<i>S</i>)-TRIP	THF (65°C)	Nd*
8	10-CSA	Toluene (80°C)	Nd*
9	L-dibenzoyl tartaric acid	Toluene (80°C)	Nd*
10	L-dianisoyltartaric acid	Toluene (80°C)	Nd*
11	L-ditoluolytartaric acid	Toluene (80°C)	Nd*
12	L-proline	Toluene (80°C)	Nd*
13	(<i>R</i>)-Mandelic acid	Toluene (80°C)	Nd*
14	TBBA	Toluene (80°C)	Nd*
15	(<i>S</i>)-TRIP	Toluene (80°C)	Nd*

* Nd: not detected

Since the synthesis of starting material **22** was irreproducible, different approaches were explored. At first, we thought the carboxylic acid was responsible for the difficulties in preparation of the compound **21**; therefore, it was protected as a methyl ester.



Scheme 8 Proposed synthesis of **26**

The nitro-acid **7** was refluxed in methanol in the presence of sulfuric acid. After simple filtration, methyl ester **23** was isolated in the 90% yield. The hydrogenation of the nitro-ester required slightly higher catalyst loading (5%) compared to the free acid nevertheless, the reaction was finished overnight and after filtration the product was isolated in the quantitative yield. The synthesis of **24** was scaled up to 20 grams scale. The acylation with TFAA in the presence of TEA in DCM at low temperature yielded trifluoroacetamide **25** in 83-90% yield at 1-gram scale.

Table 9 Chiral acid mediated cyclization of **25** to **26**

Entry	Acid	Solvent + temperature	Results
1	10-CSA	Toluene (80°C)	Nd
2	Dibenzoyl-L-tartaric acid	Toluene (80°C)	Nd
3	Dianisoyl-L-tartaric acid	Toluene (80°C)	Nd
4	Ditoluoyl-L-tartaric acid	Toluene (80°C)	Nd
5	L-proline	Toluene (80°C)	Nd
6	(<i>R</i>)-Mandelic acid	Toluene (80°C)	Nd
7	TBBA	Toluene (80°C)	Nd
8	(<i>S</i>)-TRIP	Toluene (80°C)	Nd
9	10-CSA	Toluene (120°C)	Nd
10	L-dibenzoyl tartaric acid	Toluene (120°C)	Nd
11	(<i>S</i>)-TRIP	Toluene (120°C)	Nd

Nd: not detected

Trifluoroacetamide **25** was heated in toluene in a presence of catalytic amounts of chiral acids (**Table 9**). Traces of products were observed by TLC analysis, but the conversion was very low. Similarly, no product was detected by the chiral SFC analysis after cyclization of free carboxylic acid **22**.

Due to the low reactivity of organic acids, stronger Lewis acids were tested. The cyclization catalyzed with Lewis acids could then be conducted stereoselectively in a presence of a suitable chiral ligand. 2 equivalents of Lewis acid were used. The results are summarized in **Table 10**.

Table 10 Lewis acid mediated cyclization **25** to **26**

Entry	Lewis acid	Solvent	Results
1	SnCl ₄ , 2 eq.	DCM	Complex mixture
2	TiCl ₄ , 2 eq. (1M solution)	DCM	79% isolated yield
3	Ti(OiPr) ₄ , 2 eq.	DCM	Complex mixture, low conversion

Tin tetrachloride (entry 1) and titanium isopropoxide (entry 3) yielded complex mixture of products and suffered from a low conversion of the starting material. Only the titanium tetrachloride provided full conversion of the starting material and yielded product **26** in 65% yield (entry 2). Further optimization focused on the amount of TiCl₄ in the reaction (**Table 11**).

Table 11 TiCl₄ mediated cyclization **25** to **26**

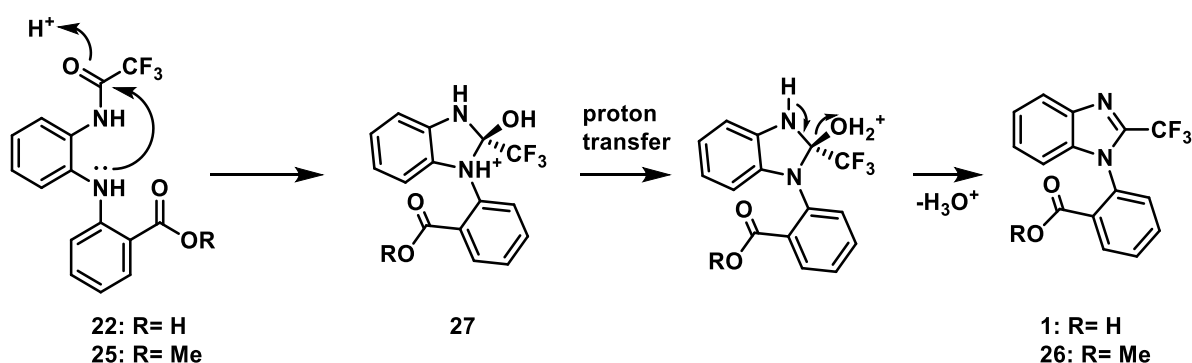
Entry	Eq. TiCl ₄	Solvent	Result
1	0.2	DCM	Traces of product
2	0.5	DCM	Traces of product
3	1	DCM	65 % isolated yield
4	1 + 1eq. (<i>R</i>)-BINOL	DCM	10% conversion ^a
5	2 + 2eq. (<i>R</i>)-BINOL	DCM	20% conversion ^a 50:50 er.

^a by HPLC

Reducing the amount of TiCl₄ provided marginal improvement. Sub-stoichiometric amounts (**Table 11**, entries 1 and 2) yielded only traces of the product while the use of 1 equivalent provided the product in 65% yield. The lower yield compared to the use of 2 equivalents (**Table 10**, entry 2) was caused by incomplete conversion of the starting material. Use of chiral (*R*)-BINOL-TiCl₄ catalyst for the cyclization severely slowed the reaction and after 24 hours only a trace conversion was observed (entry 4). Use of 2 eq. of TiCl₄ and (*R*)-BINOL provided 20% conversion of the starting material (entry 5). The product was analyzed by chiral SFC and only a racemic product was observed.

Based on the results provided by cyclization of acid **22** and ester **25**, further attempts were made to synthesize the benzimidazole core with high enantioselectivity. Based on the publications from Miller's

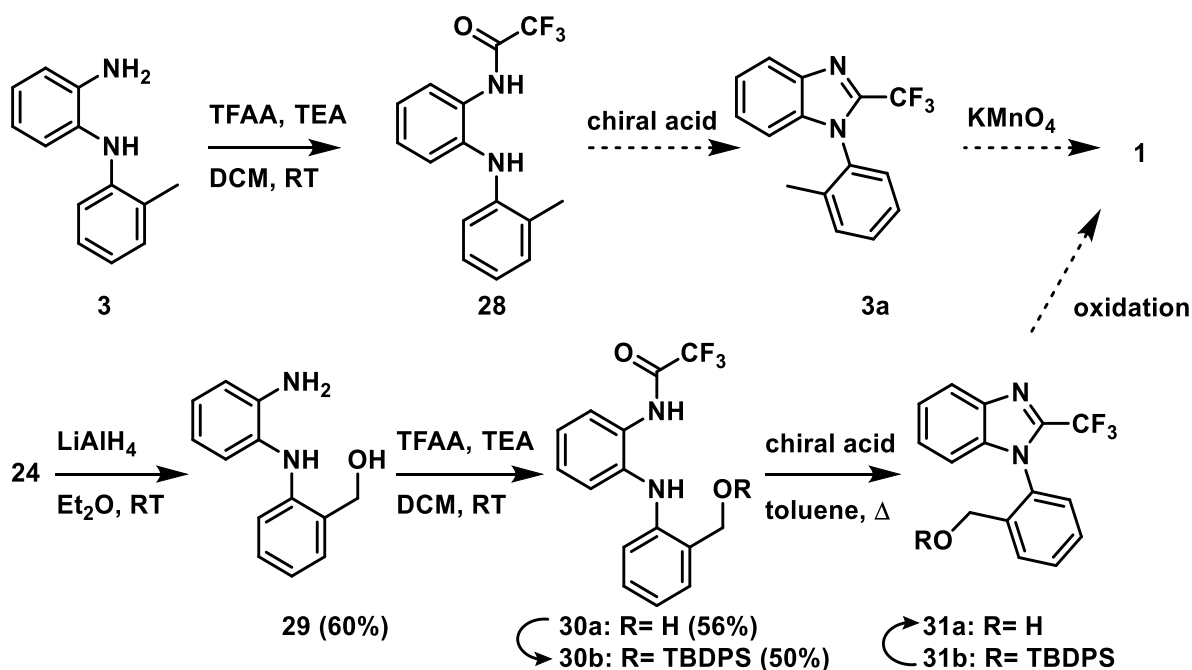
group,^{45,46} we thought the presence of the electron withdrawing group hampers the reaction by reduced nucleophilicity of the diarylamine nucleophile as is depicted in **Scheme 9**.



Scheme 9 Plausible mechanism of cyclization resulting in **1** or **26**

At first, the carbonyl group of the trifluoroacetamide is activated by the acid present in the reaction mixture and then attacked with the lone pair of the nitrogen forming intermediate **27**. This intermediate then undergoes a proton transfer and subsequent elimination of water provides final benzimidazole **1** or **26**. The first step is likely to be the slowest one and is further slowed by the conjugation of the lone pair of the nitrogen into the aromatic ring. For this reason, we attempted to modify the synthesis to include electron donating groups to further improve the reactivity (**Scheme 10**).

At first, *N*1-(*o*-tolyl)benzene-1,2-diamine **3** was acylated with TFAA in the presence of triethylamine at low temperature. The reaction proceeded smoothly to trifluoroacetamide **28**. HPLC analysis showed only one peak with correct *m/z* ratio the TLC analysis revealed a complex mixture of products. The reaction was then purified by column chromatography. No pure product was isolated and the subsequent cyclization to **3a** was not attempted. Alternatively, amino ester **24** was reduced with LiAlH₄ to yield alcohol **29** in 67% yield. **29** was further acylated with TFAA to yield amide **30a** in 20% yield which was protected with tertbutyl-diphenylsilyl to yield amide **30b** in 50% yield. Further deprotection-oxidation sequence to yield the target acid **1** was not attempted due to lack of time before finishing this thesis (**Scheme 10**).



Scheme 10 Attempt to atroposelective synthesis of **1**

The cyclization of **30a** was attempted analogously to the previously described experiments. The starting material was dissolved in toluene and a catalytic amount of the acid was added. The reaction was heated to 65°C for 16 hours. The cyclization of compound **30a** did not provide any product when the tartaric acid derivatives were used (**Table 11**, entries 1-3) while good conversion was obtained using stronger acids: 10-camphorsulphonic acid (entry 4) or BINOL-derived phosphonic acid (entry 5). SFC analysis showed encouraging atroposelectivity of the cyclization to compound **31a**. Using the 10-CSA as a catalyst yielded product in approximately 32/68 er. Unfortunately, impurity overlapping product peaks did not allow for exact integration. The absolute configuration of the product is not known.

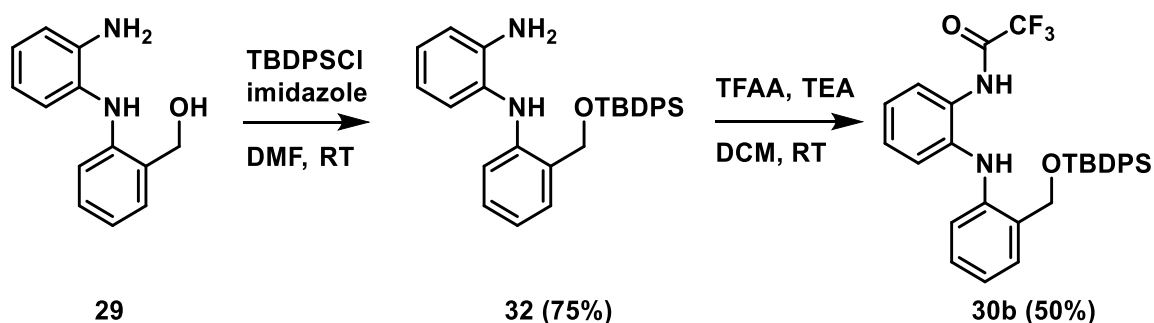
Table 11 Atroposelective cyclization of compounds **30a/b**

Entry	Starting compound	Acid	Solvent + temperature	Results
1	30a	Dibenzoyl-L-tartaric acid	Toluene 65°C	No reaction
2	30a	Dianisoyl-L-tartaric acid	Toluene 65°C	No reaction
3	30a	Ditoluoyl-L-tartaric acid	Toluene 65°C	No reaction
4	30a	(<i>S</i>)-TRIP	Toluene 65°C	Er. 73/27
5	30a	10-CSA	Toluene 65°C	Er. 32/68*
6	30b	(<i>S</i>)-TRIP	Toluene 65°C	decomposition

* Overlapping integrals in SFC, the value is approximate

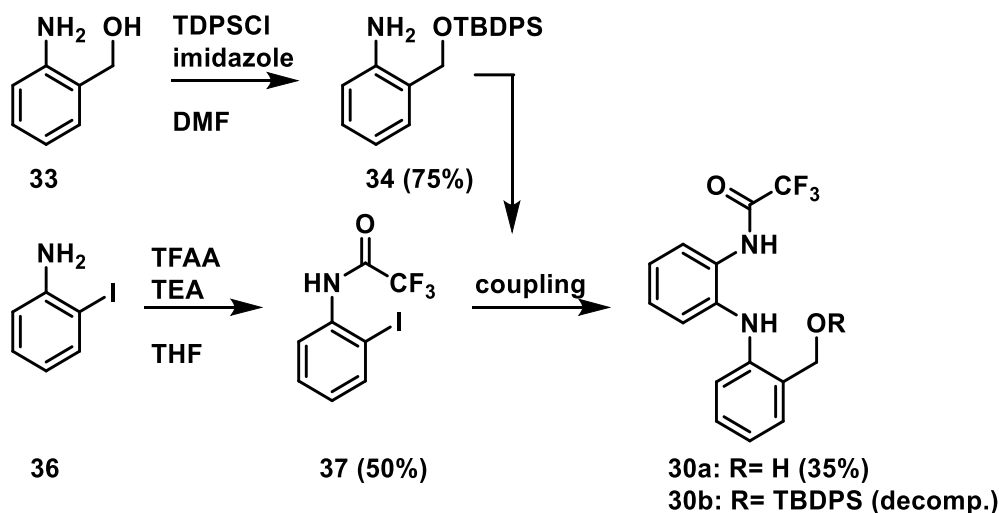
Since the cyclization experiments were limited by the amount of starting materials **30a** or **30b** which could not be reliably prepared in reasonable amounts for the application, alternative pathways leading towards those compounds were explored. Firstly, different acylation conditions (TFA+T3P or TFA+DCC) were used; however, no product was formed. Following those failures, different approaches

were explored (**Scheme 11-12**). Benzyl alcohol **29** was protected with TBDPSCI to yield compound **32** using slight excess of TBDPSCI and imidazole as a base. Compound **32** was isolated in 75% yield after column chromatography. TBDPS protected amino alcohol was then acylated with TFAA and the product was isolated in 50% yield after column chromatography. Unfortunately, the reaction was not completed even after subsequent additions of more TFAA.



Scheme 11 Alternative synthesis of compound **30b**

Alternatively, the benzyl alcohol **33** was protected with TBDPS to yield **34** in 75% yield after chromatography. 2-Iodoaniline **36** was acylated with TFAA to yield **37** in various yields: previously performed acylation in DCM yielded product in 50% yield, but exchange of the solvent to THF improved the yield to 95%.¹⁵¹



Scheme 12 Synthesis of **30a/b** by metal-catalyzed coupling reaction

Amines **33** and **34** were there coupled to the TFA-protected iodoaniline **37** under various conditions. Results are summarized in **Table 12**. Product **30a** was isolated in 25% yield using the previously reported conditions (entry 1).⁴⁵ The increase of the reaction scale from 0.2 mmol to 1 mmol (entry 2) slightly increased the yield but still not sufficient. The change from copper to palladium catalysis with

XPhosPdG2 did not provide any improvements although the used catalyst was used with a great success in our research group.¹⁵² Arylation of protected benzyl alcohol **34** and copper catalyst (entry 4) did not work at all and a complete decomposition was observed.

Table 12 Synthesis of **30a/b** by metal catalyzed coupling reaction

Entry	Amine	Conditions	Results
1	33	CuI 10%, 2,2'-biphenol 10%, K ₃ PO ₄ , DMF, ACN, 60°C ⁴⁵	25% yield
2	33	CuI 10%, 2,2'-biphenol 10%, K ₃ PO ₄ , DMF, ACN, 60°C, 1 mmol scale	35% yield
3	33	XPhosPdG2 2%, K ₃ PO ₄ , dioxane	No reaction
4	34	CuI 10%, biphenol 10%, K ₃ PO ₄ , DMF, ACN, 60°C	decomposition

Since the coupling approach towards compound **30** was not very successful and the cyclization itself provided products only in a modest enantiomeric excess combined with the difficulties of the preparation of the starting materials, this approach was abandoned in favor of the synthesis of racemic TBBA and further resolution.

3.4. Conformational stability of TBBA

Since the most common mechanism of racemization of axially chiral compounds is a simple bond rotation, the stability of TBBA was tested. TBBA was heated at various temperatures in various solvents to determine the rate of racemization. The results are summarized in **Table 13** and **14**.

Table 13 Conformational stability of TBBA in alcohols

Entry	Solvent	Temperature	Time (h)	%ee
1	MeOH	60°C	5	100
2	MeOH	60°C	8	100
3	MeOH	60°C	16	98
4	BuOH	80°C	5	96
5	BuOH	80°C	8	84
6	BuOH	80°C	16	82

At first, racemization was investigated in MeOH at 60 °C. Even after prolonged heating, no racemization was observed (**Table 13**, entries 1-2) with a slight drop in enantiomeric purity after 16 hours (entry 3). Higher temperature at 80 °C increased the rate of racemization as expected and slight racemization was observed already after 5 hours (entry 4). The enantiomeric purity further decreased to 82% ee (entry 6). The temperature was further increased to accelerate racemization. The solvent was changed to higher boiling ethylene glycol (**Table 14**).

Table 14 Racemization kinetics of TBBA in ethylene glycol

Temperature	Time (min)	%ee	k_{rac}	$\Delta G_{\text{rac}}^{\ddagger}$ (kcal/kJ)	$t_{1/2}$ (min)
100°C	10	99.42	1.27×10^{-5}	30.37 / 127.05	906.1
	20	98.90			
	30	98.24			
	60	96.04			
	90	93.82			
	120	91.54			
	180	87.12			
	240	82.78			
	300	78.86			
	360	74.90			
	420	70.66			
	1620	24.48			
	1740	22.30			
	1860	19.94			
	2880	8.48			
	3000	7.68			
3180	6.20				

At first, the racemization was conducted at 100 °C. Full racemization was observed after 3180 minutes (53 hrs.) with the half-life of the racemization being 906 minutes (approx. 15 hours). Then, the temperature was increased to 140 °C and, as expected, the racemization was significantly faster and full racemization (%ee < 1%) was observed after 160 minutes. (Table 15) and the half-life being calculated to 25 minutes.

Table 15: Racemization kinetics of TBBA in ethylene glycol

Temperature	Time (min)	%ee	k_{rac}	$\Delta G_{\text{rac}}^{\ddagger}$ (kcal/kJ)	$t_{1/2}$ (min)
140°C	10	84.08	4.56×10^{-4}	30.77 / 128.73	25.3
	20	64.22			
	30	48.06			
	40	36.0			
	50	27.16			
	60	20.34			
	70	15.26			
	80	11.36			
	90	8.48			
	100	6.28			
	110	4.64			
	120	3.54			
	130	2.44			
	140	1.64			
	150	1.24			
	160	0.94			
	170	0.42			
180	0.38				
190	0.18				
25°C	---	---	3.42×10^{-10}	30.37 / 127.05	64.2 years

From the data depicted in **Tables 14** and **15**, racemization kinetics were calculated using equations 1-3 (**Figure 7**).

Eq. 1
$$\ln\left(\frac{R_0}{R_0 - x}\right) = k_{\text{rac}}t$$

Eq. 2
$$\Delta G_{\text{rac}}^{\ddagger} = -RT \ln\left(\frac{hk_{\text{rac}}}{\kappa T k_{\text{B}}}\right)$$

Eq. 3
$$\tau_{1/2\text{rac}} = \frac{\ln 2}{k_{\text{rac}}}$$

R_0 = initial concentration of the enantiomer, x = concentration of the racemate at time t , h = Planck constant, k_{B} = Boltzmann constant, κ = transmission coefficient (equals to 1), T = temperature, R = gas constant, k_{rac} = racemization rate constant, $\Delta G_{\text{rac}}^{\ddagger}$ = energy barrier for racemization, $\tau_{1/2\text{rac}}$ = half-life of racemization

Figure 7 Equations used for calculation of racemization kinetics

At first, **Equation 1** was used to calculate racemization rate constant k_{rac} (average k_{rac} shown in **Tables 14-15**). This rate constant was then used to calculate the energy barrier of rotation $\Delta G_{\text{rac}}^{\ddagger}$ (**Equation 2**) and the half-life of racemization $t_{1/2}$ (**Equation 3**). The lower $\Delta G_{\text{rac}}^{\ddagger}$ (i.e., lower rotation barrier therefore lower stability) obtained from data at 100°C was used to calculate the half-life at the room temperature. The calculated half-life at room temperature was 64 years, which makes TBBA sufficiently stable to store at laboratory/room temperature.

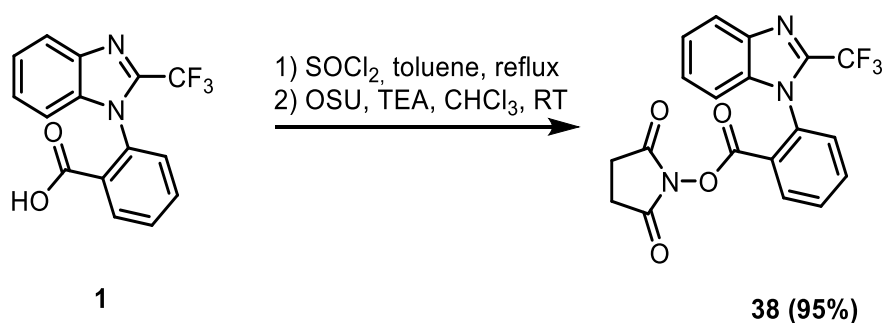
3.5. NMR results

3.5.1. Analysis of α -chiral amines and alcohols

Based on the NMR spectra of amide **11** prepared from racemic TBBA and enantiopure amine, it was evident that TBBA can differentiate NMR signals between the enantiomers. For the configuration assignment, a conformational model had to be described based on the NMR spectra of tested derivatives. Furthermore, a mild acylation procedure had to be developed. At first, acylation of amines via acid chloride (TBBA-Cl) was performed using the already described procedure of heating the enantiopure TBBA in toluene at 110°C in a presence of SOCl_2 . The reaction is very fast and was complete within five minutes of heating. The time of heating was very important: longer heating times caused partial racemization as is evident from the racemization experiments (**Table 14**). Luckily, the reaction could be monitored visually: TBBA is not fully dissolved in the mixture of toluene and SOCl_2 at room temperature and slowly dissolves during heating. It was observed, that when the reaction mixture becomes clear solution, the formation of acyl chloride is complete.

The acylation of amines was then performed by slow addition of the solution of TBBA-Cl in CHCl_3 to the solution of the amine and trimethylamine in CHCl_3 . Usually, the reaction was complete within one hour and, in most cases, a product was isolated by simple acid-base extraction. Although the acyl chloride method worked well, alternative methods were explored to a) reduce the risk of racemization to the absolute minimum and b) to possibly eliminate the need of additional work before the acylation (i.e., preparation of fresh TBBA-Cl before each reaction).

At first, the isolation of TBBA-Cl was attempted by precipitation in hexanes; nevertheless, the TBBA-Cl was always isolated as a brown oil, which complicated the weighing of the required amounts for the reaction. Second, TBBA-Cl was converted into an OSU (N-hydroxysuccinimide) ester **38**¹⁵³ (**Scheme 13**), which could then act as an active acylation species in the reaction.



Scheme 13 Synthesis of OSU ester **38**

The OSU ester was obtained in the high yield (96%) starting with racemic **1** after simple extraction on a gram scale and its utility as an acylation species was tested. The results are shown in **Table 16**. Simple stirring of the compound **38** with the amine in CHCl_3 at room temperature overnight yielded 80% conversion with the remaining 20% of reaction mixture was the unreacted starting material (entry 1). Simple addition of base caused full conversion to the product which was isolated in 90% yield after acid-base extraction (entry 2).

Table 16 Acylation of amines with OSU ester **38**

Entry	Amine	Conditions	Results
1	(<i>R</i>)-phenylethylamine	CHCl_3 , no base, RT, 18 hrs.	80% conversion ^a
2	(<i>R</i>)-phenylethylamine	CHCl_3 , triethylamine, RT, 18 hrs.	90% yield

^a by HPLC

While the reaction worked well with racemic TBBA, the conversion of enantiopure TBBA to the OSU ester was more complicated. The preparation of TBBA-Cl on a small scale (<50 mg) and further conversion to **38** worked well. The scale-up of the reaction proved to be more complicated. This was mainly because the formation of the TBBA-Cl took longer time at larger scale and, subsequently, approx. 10% racemization was observed. For this reason, milder methods were investigated. The use of the EDCI in DMF¹⁵⁴ did not yield the product at all. The direct acylation with TBBA in the presence of EDCI and hydroxybenzotriazole (HOBt) in DMF worked and produced the desired amides after simple acid-base extraction without the need of the intermediate **38**, which clearly simplified the procedure. At first, the set of amides was prepared (Figure 8) using EDCI+HOBt in DMF.^{155,156} All amines were acylated with both enantiomers of TBBA.

3.5.1.1. ¹H-NMR analysis

Compounds **39-50** were prepared in 50-98% yields after column chromatography. The shielding effects are displayed as $\Delta\delta^{PM}$. $\Delta\delta^{PM}$ is calculated by subtraction of the chemical shift of the given signal in the *M*-diastereomer from the chemical shift of the same signal in the *P*-diastereomer:

$$\Delta\delta^{PM} = \delta\text{L1}(P) - \delta\text{L1}(M)$$

If the $\Delta\delta^{PM} < 0$, the given proton is shielded in the *P*-diastereomer and analogously, if $\Delta\delta^{PM} > 0$ is deshielded in the *P*-diastereomer. This information then allows to locate the given substituents in space to deduce the correct configuration with the aid of the conformational model (*vide infra*).

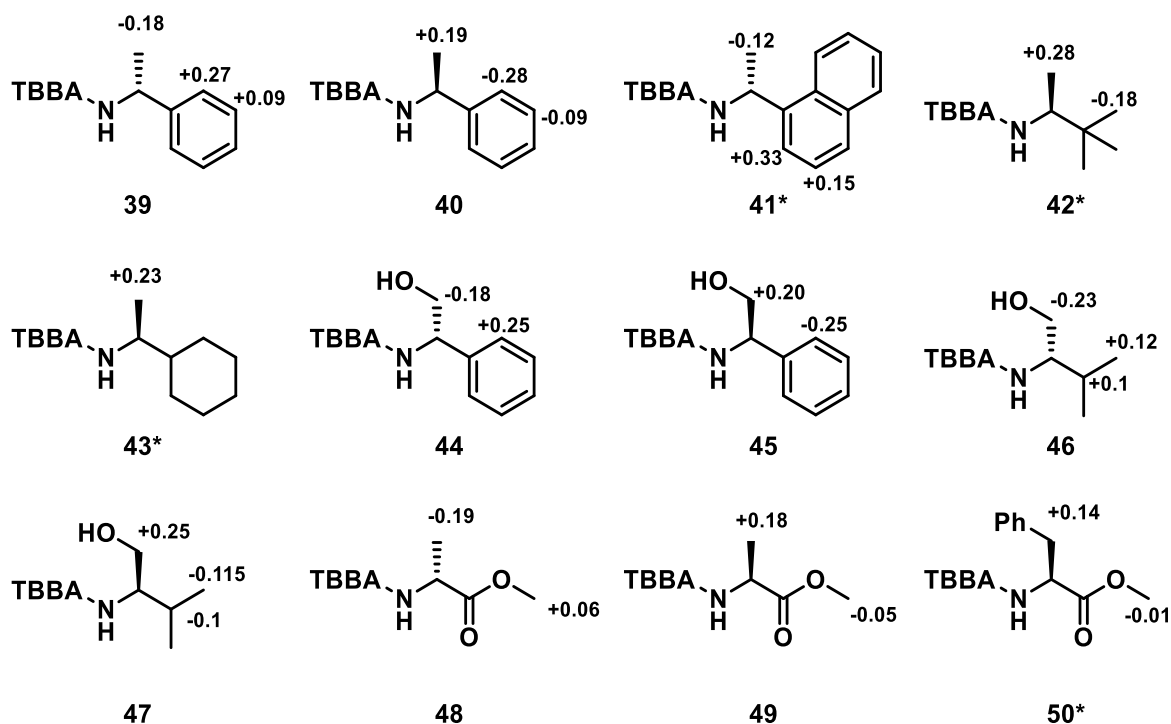


Figure 8 Observed $\Delta\delta^{PM}$ for compounds 39-50

*Compound **50** was prepared by undergraduate student David Profous.

At first, phenethylamines were acylated with TBBA yielding compounds **39** and **40** (Figure 8). Both enantiomers of phenethylamine were separately analyzed to compare the differences between the enantiomers of the amine. As can be seen, the $\Delta\delta^{PM}$ of compounds **39** and **40** are identical in magnitude with the slight difference of 0.01 ppm which can be attributed to the limit of the method. As expected, the sign of the $\Delta\delta^{PM}$ were reversed due to the opposite configuration of tested amines. The most relevant signals of **39** (i.e., the closest to the chiral center) showed -0.18 ppm of the methyl group and +0.27 and +0.09 ppm for the aromatic *ortho* and *meta* protons. The analysis of compounds which possess aromatic rings close to the chiral center could be complicated and yield anomalous values;¹⁵⁷ nevertheless, none anomalous values were observed. Moreover, the magnitude of the $\Delta\delta^{PM}$ of the methyl group was significantly higher than in the case of MTPA (0.04), MPA (0.07), or MPA in the complex with BaClO₄ (0.09).^{88,158,159}

Substitution of the phenyl ring for the larger naphthyl ring in **41** had a slight effect on the $\Delta\delta^{PM}$. The $\Delta\delta^{PM}$ of the methyl group (-0.12) was slightly lower compared to **39** and **40** but higher compared to

MPA (0.07)¹⁵⁹ and slightly smaller compared to Boc-phenylglycine (BPG) (0.17).⁷⁰ The aromatic protons showed slightly higher $\Delta\delta^{PM}$ compared to **39** and **40**. The nonaromatic amines **42** and **43** showed high $\Delta\delta^{PM}$ for the methyl group: +0.28 and +0.23 for **42** and **43** respectively.

Phenylglycinol was acylated under the same conditions without any detected *O*-acylation in the reaction mixture. Addition of the polar hydroxyl group in **44** and **45** did not have a significant effect on the observed $\Delta\delta^{PM}$ compared to non-hydroxylated derivatives **39** and **40**. The homobenzylic protons in **44** displayed -0.18 ppm, which was very similar to the homobenzylic protons in **39**. The protons in the *ortho* position showed +0.25 ppm difference, which was similar to the same protons in **39**. The same behavior was observed with the enantiomeric amino alcohol **45**.

Substitution of the phenyl group for the more branched and sterically demanding isopropyl group in **46** and **47** slightly increased the $\Delta\delta^{PM}$ of the hydroxymethyl group compared to phenylglycinol derivatives. The isopropyl group showed significantly lower $\Delta\delta^{PM}$ (+0.12 and +0.1), but still sufficiently higher above the experimental limits of the method. Enantiomeric amide **47** displayed slightly higher (0.02 ppm) $\Delta\delta^{PM}$ compared to **46** while the $\Delta\delta^{PM}$ of the isopropyl group was pretty much same as expected.

The $\Delta\delta^{PM}$ of the methyl group in the alanine derivatives **48** and **49** showed -0.19 and +0.18 ppm, respectively, on a par with the phenethylamines **39** and **40** and phenylglycinols **44** and **45**, but slightly lower than the aliphatic amides **42**, **43**, **46**, and **47**. The $\Delta\delta^{PM}$ of the methyl ester was significantly smaller (+0.06 and -0.05), which was expected due to the group being located further away from the chiral center. The observed values were higher compared to MTPA (0.08 for the methyl and 0.03 for the methyl ester).¹⁵⁹ As expected, a comparison of enantiomers **48** and **49** shows no significant differences.

The phenylalanine derivative **50** showed lower $\Delta\delta^{PM}$ compared to the alanine derivatives (+0.14 vs +0.18) and the methyl ester displayed only minimal 0.01 ppm difference. Compared to BPG⁷⁰ and MPA⁸⁸ the $\Delta\delta^{PM}$ of the benzylic proton was roughly the same (0.14 vs 0.18 and 0.08 respectively) while the $\Delta\delta^{PM}$ of the methyl ester was significantly lower (-0.01 vs 0.11 and 0.07 respectively).

Furthermore, esters **51-59** (**Figure 9**) were prepared in 50-86% yields. Different acylation conditions were used for synthesis of esters: dicyclohexylcarbodiimide (DCC) and dimethylaminopyridine (DMAP) in DCM. Although the dicyclohexylurea precipitated from the reaction mixture and was filtered away, column chromatography was necessary to use for all compounds.

Ester **51**, an analogue of **39**, displayed significantly higher $\Delta\delta^{PM}$ values. The difference at the methyl group showed -0.32 ppm which was almost a double value compared to **39** (-0.18). Analogously, the $\Delta\delta^{PM}$ of the proton at the *ortho*-position of the phenyl ring was significantly higher compared to **39** (+0.45 vs +0.27) and MPA and MTPA (0.06 and 0.08 respectively). Only 9-AMAA showed comparable differentiation (0.3 ppm).⁹¹ The substitution of the phenyl ring for aliphatic ethyl at **52** showed a slight

increase in the $\Delta\delta^{PM}$ of the methyl group (+0.49) while the ethyl group displayed high $\Delta\delta^{PM}$ difference on both the methyl and methylene protons. Further substitution of the ethyl for the more rigid ethynyl at **53** lowered the $\Delta\delta^{PM}$ on both the methyl group (+0.26 vs +0.49 at **52**) and the terminal alkyne (-0.28 vs -0.33 terminal methyl at **52**). Compared to MPA, the $\Delta\delta^{PM}$ at **53** were significantly higher (0.207 and 0.086).¹⁰⁰

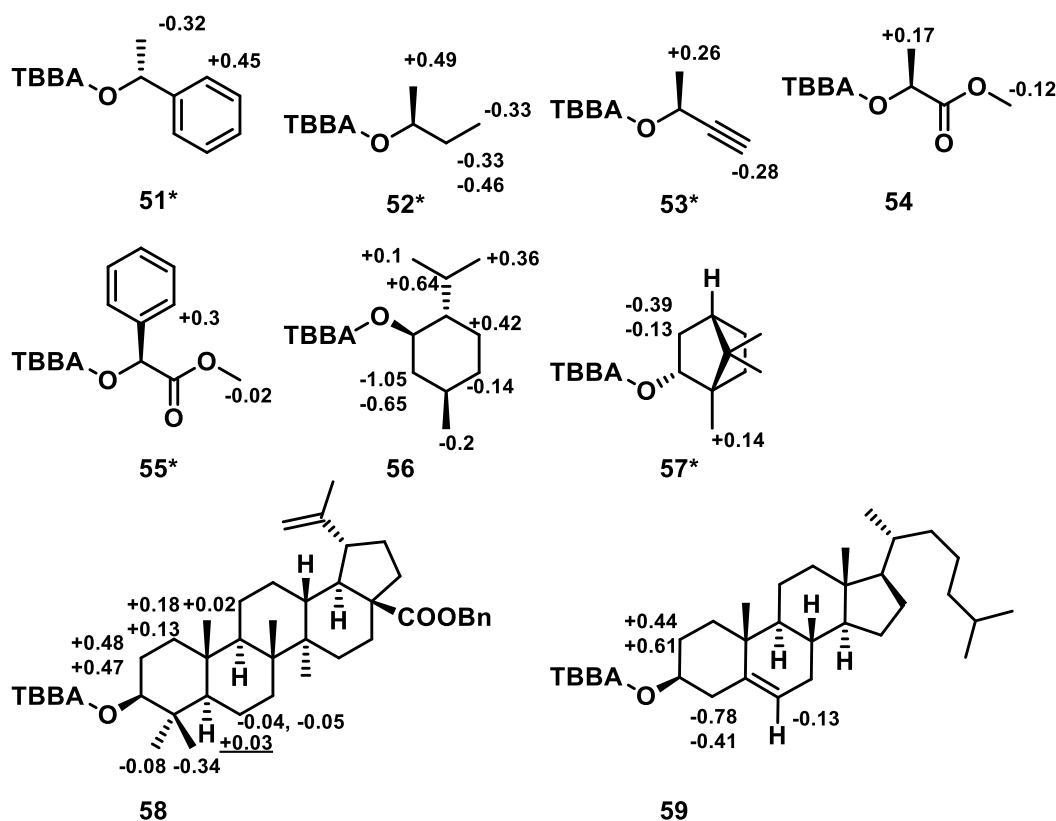


Figure 9 Observed $\Delta\delta^{PM}$ for esters **51-59**

*Compound was prepared by undergraduate student David Profous

Further substitution of the aliphatic chains for the carboxymethyl in **54** caused further decrease of the observed $\Delta\delta^{PM}$. The $\Delta\delta^{PM}$ of the methyl group decreased from the +0.49 and +0.26 for **52** and **53** to +0.17 but stayed like the alanine derivative **49**. Interestingly, the $\Delta\delta^{PM}$ of the methyl ester was -0.12 which was significantly higher compared to alanine **49** (-0.05) and phenylalanine **50** (-0.01). The difference was also comparable to the MPA ester prepared from lactic acid: 0.075 ppm for methyl and 0.17 ppm for the carboxymethyl group.¹⁰⁰ Further substitution of the methyl group for the phenyl significantly reduced the $\Delta\delta^{PM}$ of the methyl ester: -0.02 in **55** compared to -0.12 in **54**. The $\Delta\delta^{PM}$ of the phenyl is slightly lower compared to the phenyl substituted ester **51**. The difference are also smaller compared to MPA and 9-AMAA esters.^{91,100}

In addition, L-menthol TBBA esters **56** were prepared because menthol often serves as a model compound for new CDAs.^{86,160–162} The observed $\Delta\delta^{PM}$ of the isopropyl group (+0.1 and +0.36) were smaller compared to the 9-AMAA ester. The $\Delta\delta^{PM}$ of the methyl group at position 5 was slightly higher compared to 9-AMAA (0.2 vs 0.1 ppm).⁸⁹ The $\Delta\delta^{PM}$ at the position 3 (-1.05 and -0.65 ppm) were unexpectedly high and even the differences at more remote positions 5 (-0.14) and 6 (+0.42) exceeded 0.1 ppm. Interestingly, the structurally similar borneol **57** displayed smaller $\Delta\delta^{PM}$ compared to menthol **56**. The difference at position 3 was -0.13 and -0.39 ppm and the methyl group at position 1 displayed +0.14 ppm which was on the same level as the MPA ester and smaller compared to the 9-AMAA ester.⁹¹

Lastly, two natural products derivatives were tested: benzyl betulinate **58** and cholesterol **59**. The derivative **58** displayed high $\Delta\delta^{PM}$ on the A-ring (+0.48, +0.47, +0.18 and +0.13) and the adjacent methyl groups (-0.08 and -0.34). The differences were observable even at the remote position 6 (-0.04 and 0.05) and the methyl at position 25 (+0.02). This was likely due to the high rigidity of the steroidal structure which allows clear projection of the shielding effect on the remote positions. The proton at position 5 displays anomalous sign of the $\Delta\delta^{PM}$; however, this anomaly can be ignored due to the low magnitude of the difference and the fact that the remaining protons differences show homogenous signs. Cholesterol **59** was previously derivatized with MTPA.¹⁵⁸ TBBA differences on the A-ring (+0.44, +0.61, -0.41 and -0.78) were significantly higher compared to MTPA (-0.06, +0.09 and +0.09).

3.5.1.2. ¹³C NMR analysis

In addition, ¹³C NMR spectra were analyzed as well. Compared to ¹H, the use of ¹³C for the configuration assignment is limited. This limitation comes from the two major factors: a) larger amounts of sample and time are required to obtain high quality ¹³C NMR spectra and b) the $\Delta\delta^{RS}$ values observed in the ¹³C spectra are in most cases small when the whole scale (0-200 ppm) of the ¹³C NMR spectrum is considered.⁸⁷ Nevertheless, modern NMR techniques allow to obtain high quality NMR spectrum even from tiny amounts of sample.

To our delight, the analyzed ¹³C $\Delta\delta^{PM}$ data followed the general trend observed in the ¹H spectra. The easily distinguishable methyl groups in compounds **39-43**, **48-49** showed ¹³C $\Delta\delta^{PM}$ absolute values between 0.14 and 0.4 ppm. The methylene signals in **51-54** displayed differences 0.3 and 0.33 ppm. On the other hand, the methylene carbons in **50** were shifted by 0.08 ppm. Most importantly, the alkynyl carbon in **53** without protons demonstrated a difference of 0.45 ppm. Furthermore, in accordance with the general trend, the more remote methyl ester signals in **48-50**, **54-55** displayed low ¹³C $\Delta\delta^{PM}$ values ranging from 0.04 (compounds **13**, **14**) to 0.06 (compounds **18**, **19**) ppm. Even though the observed values are small considering the entire ¹³C NMR chemical shift range, in most cases, the $\Delta\delta^{PM}$ value was high enough to assign the absolute configuration, especially, when results were combined with the ¹H chemical shifts.

3.5.1.3. Conformational model for assignment of absolute configuration by ^1H or ^{13}C NMR

Not only were the NMR differences higher compared to most of the common reagents, but more importantly, they followed a clear trend. Based on the data, the conformational model was devised, which allows for assignment of the absolute configuration of tested compounds (**Figure 10**).

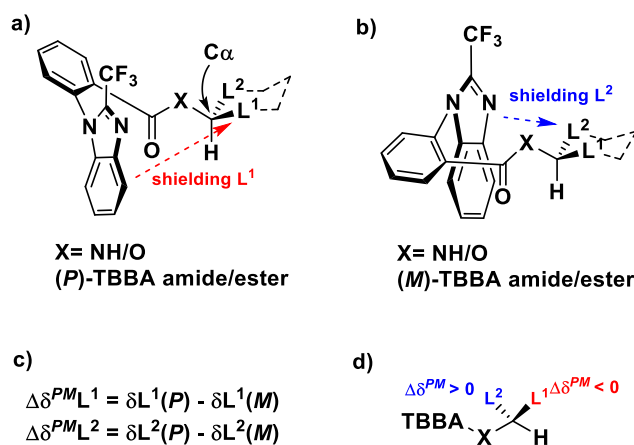


Figure 10 Model for the assignment of the absolute configuration if chiral secondary alcohols and primary amines a) (*P*)-TBBA amide/ester b) (*M*)-TBBA amide/ester c) calculation of $\Delta\delta^{PM}$ d) simplified model

In this proposed model, the benzimidazole and phenyl rings are perpendicular to each other. The carbonyl group is oriented opposite compared to the trifluoromethyl group. The proton at $\text{C}\alpha$ is in *syn*-periplanar position to the carbonyl group which orients one of the substituents L^1 and L^2 in front of the benzimidazole ring, which projects the shielding effect on this substituent (**Figure 10a/10b**). This projected shielding effect causes the chemical shift of the substituent to be shifted upfield. In the example in **Figure 10**, assuming the displayed configuration, substituent L^1 in the (*P*)-derivative (**Figure 10a**) is going to have lower chemical shift compared to the L^1 in the (*M*)-derivative (**Figure 10b**). Analogously, the chemical shift of the L^2 substituent in the (*P*)-derivative is going to be higher compared to the same substituent in the (*M*)-derivative.

These changes on chemical shifts can be expressed as the $\Delta\delta^{PM}$ parameter, which was calculated according to equation shown in Figure 10c. Based on the observed $\Delta\delta^{PM}$ values, the substituents L^1 and L^2 can then be located in space and absolute configuration can be deduced. If the substituent has a negative $\Delta\delta^{PM}$ value (as does L^1 in **Figure 10**), it is located above the plane of coplanar amide/ester function and $\text{C}\alpha$. If the substituent possesses a positive $\Delta\delta^{PM}$ value (as does L^2 in **Figure 10**), it is located below the plane. The simplified model is shown in **Figure 10d**.

To further confirm our model, series of in-silico simulations using Spartan 16 software were performed. The population of theoretical conformers was calculated with the molecular mechanics model MMFF. Depending on the total number of theoretical conformers, this was followed by sorting

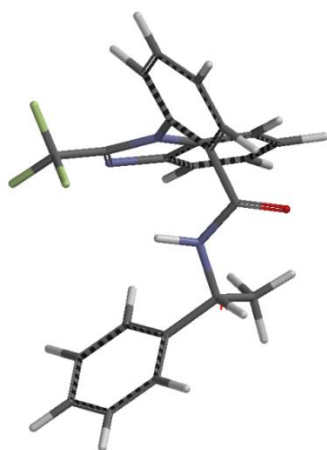
of the conformation candidates with relative energies lower than 10–20 kJ/mol. The energies of sorted candidates at the ground state in the nonpolar solvent were calculated using density functional theory (B3LYP, 6-31G*) to find the lowest energy conformer.

The calculation revealed that over 99% of diastereomer (**P**)-**39** was distributed over four conformers with Boltzmann weights of 0.414, 0.276, 0.186, and 0.120. The most stable conformer (**Figure 11a**) (Boltzmann weight 0.414) is not relevant for the NMR experiments since the molecule is rotated in a way where both substituents are in the shielding zone of the benzimidazole. This means, the shielding effect is not produced selectively and, in the end, both substituents would have their chemical shifts moved upfield and therefore no difference in the NMR spectra can be expected. We assumed the second most stable theoretical conformer (**Figure 11b**) of (**P**)-**39** (Boltzmann weight 0.276, $\Delta G = +1.01$ kJ/mol) was the most NMR-significant one since the anisotropic effect of the benzimidazole moiety is preferentially space-oriented and efficient toward the methyl group. As proposed in the model, the C α and carbonyl group are *syn*-periplanar.

The remaining two conformers (**Figure 11c/d**) with Boltzmann weights 0.186 and 0.120 ($\Delta G = +1.99$ kJ/mol and 3.06 kJ/mol) were not NMR relevant since both substituents are located outside of the shielding zone and therefore, no observable change in the NMR spectra can be expected.

Compound (**P**)-**39**

a)



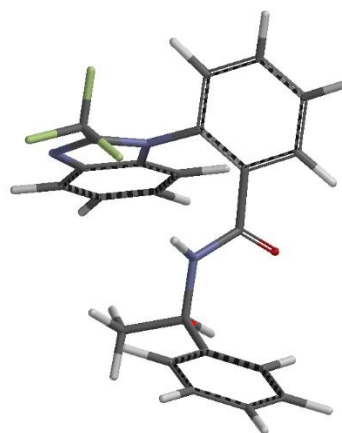
Most stable conformer

Boltzmann weight: 0.414

NMR insignificant: non-selective shielding of both substituents at the same time

c)

b)

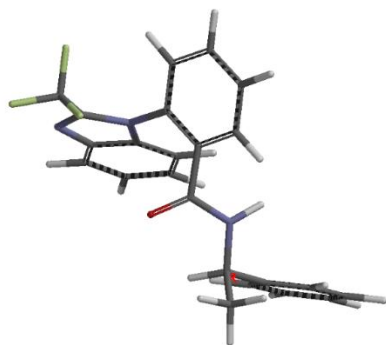


2nd most stable $\Delta G = +1.01$ kJ/mol

Boltzmann weight: 0.276

NMR relevant: selective shielding on methyl substituent

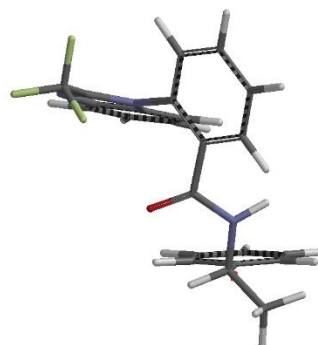
d)



3rd most stable $\Delta G = +1.99$ kJ/mol

Boltzmann weight: 0.186

NMR insignificant: shielding effect is not produced on any of the substituents



4th most stable $\Delta G = +3.06$ kJ/mol

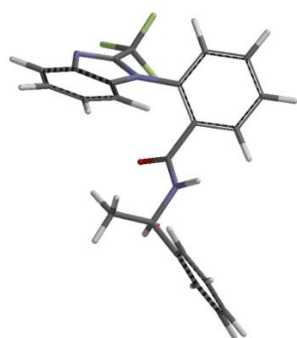
Boltzmann weight: 0.120

NMR insignificant: shielding effect is not produced on any of the substituents

Figure 11 Conformers of compounds (*P*)-39

The calculations revealed that most of the conformation equilibria of the diastereomer (*M*)-39 consisted of only two conformers (total Boltzmann weight 0.978). The major conformer (Boltzmann weight 0.60), which is similar to (*P*)-39, is not NMR relevant since none of the substituents are in the shielding zone of the benzimidazole ring. The less stable conformer (**Figure 12b**) (Boltzmann weight 0.378, $\Delta G = +1.15$ kJ/mol) was considered as the NMR relevant conformer with the phenyl ring being directly in the shielding zone of the benzimidazole with complete accordance to the experimental data.

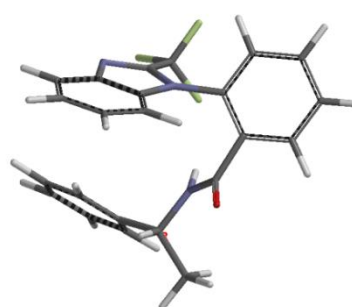
Compound (*M*)-39



a) Most stable conformer

Boltzmann weight: 0.60

NMR insignificant: shielding effect is not produced on any of the substituents



b) 2nd most stable $\Delta G = +1.15$ kJ/mol

Boltzmann weight: 0.378

NMR relevant: shielding effect produced selectively on phenyl substituent

Figure 12 Conformers of compounds (*M*)-39

3.5.1.4 ^{19}F -NMR analysis

Attempts to correlate the ^{19}F spectra with the absolute configuration were conducted as well. The ΔCF_3 was calculated analogously to the $\Delta\delta^{PM}$ parameter using following equations:

$$\Delta\text{CF}_3 = \delta\text{L1}^{19\text{F}}(P) - \delta\text{L1}^{19\text{F}}(M)$$

by subtracting the chemical shift of the ^{19}F spectrum of the (*M*)-diastereomer from the ^{19}F spectrum of the (*P*)-diastereomer. The results are summarized in **Figure 13** and **14**.

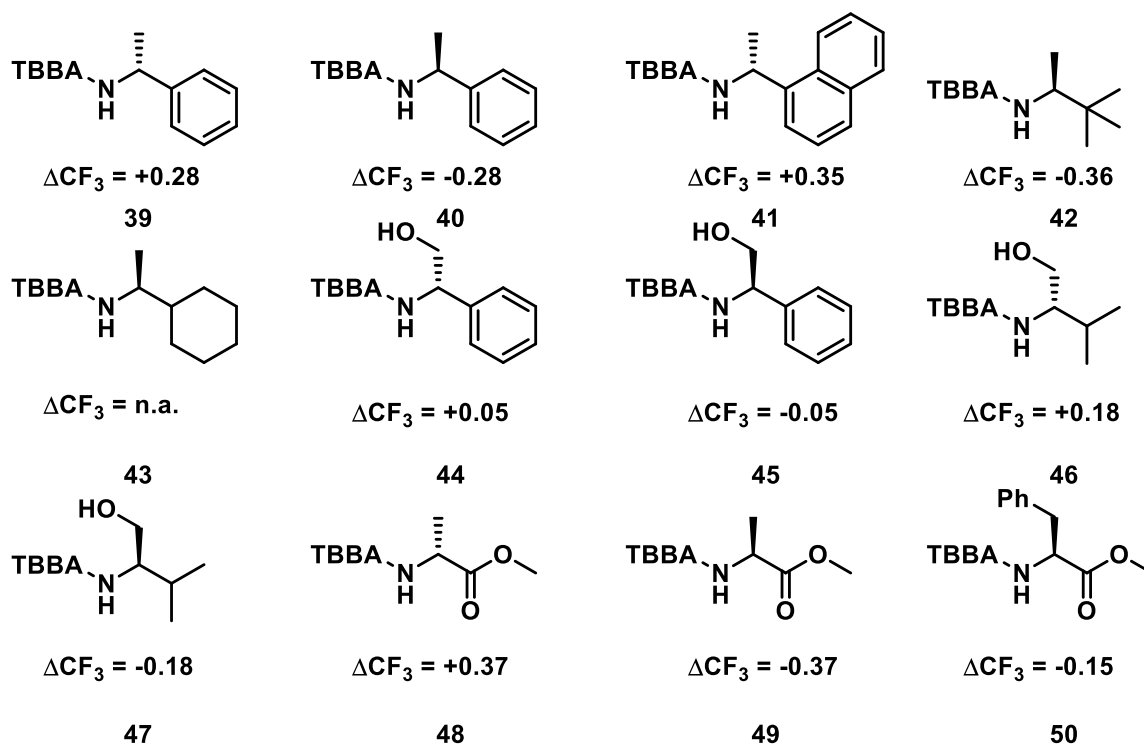


Figure 13 Observed ΔCF_3 for amides **39-50**, n.a.: not available

At first, the ^{19}F NMR spectra of the TBBA-amides **39-50** were analyzed (**Figure 13**). The amides **39** and **40** displayed 0.28 ppm difference and, as expected, the sign was reversed for the **40** compared to **39**. Changing the phenyl ring of **39** for a larger naphthyl ring in **41** slightly increased the ΔCF_3 to +0.35 ppm. Moreover, the positive sign was same as observed for **39** with the same absolute configuration. Further changing the aromatic moiety for aliphatic in **42** did not have a significant effect on the ΔCF_3 . Addition of the polar hydroxyl group caused a significant difference and lowered the ΔCF_3 to 0.05 in **44** and **45** and to 0.18 in **46** and **47**. Modification of the structure by addition of the carboxymethyl group in **48** and **49** displayed a similar ΔCF_3 to aryl derivatives **39-41**. Substitution of the methyl group for benzyl in **50** slightly lowered the ΔCF_3 from -0.37 to -0.15 in **49**.

Compound **51** displayed a significantly lower ΔCF_3 compared to aza-analogue **39**: +0.02 vs +0.28. The substitution of the phenyl group for ethyl in **52** displayed a slightly higher ΔCF_3 (-0.18) as was

observed in similar aliphatic aza-derivative **42**. The substitution of the ethyl group for the ethynyl in the ester **53** displayed not only smaller ΔCF_3 (+0.07) but also the positive sign of the ΔCF_3 . This was in the stark contrast to other compounds where the trend would suggest negative ΔCF_3 for compound **53**. Further addition of carboxymethyl group in **54** showed a similar ΔCF_3 in magnitude as in alkynyl derivative **53** although, this time with expected negative sign of the ΔCF_3 . Substitution of the methyl group for phenyl in compound **55** showed comparable ΔCF_3 (-0.17) to **52**. The addition of a carboxymethyl group caused significant change in the magnitude of the ΔCF_3 value as compared to **51** (-0.17 vs 0.02).

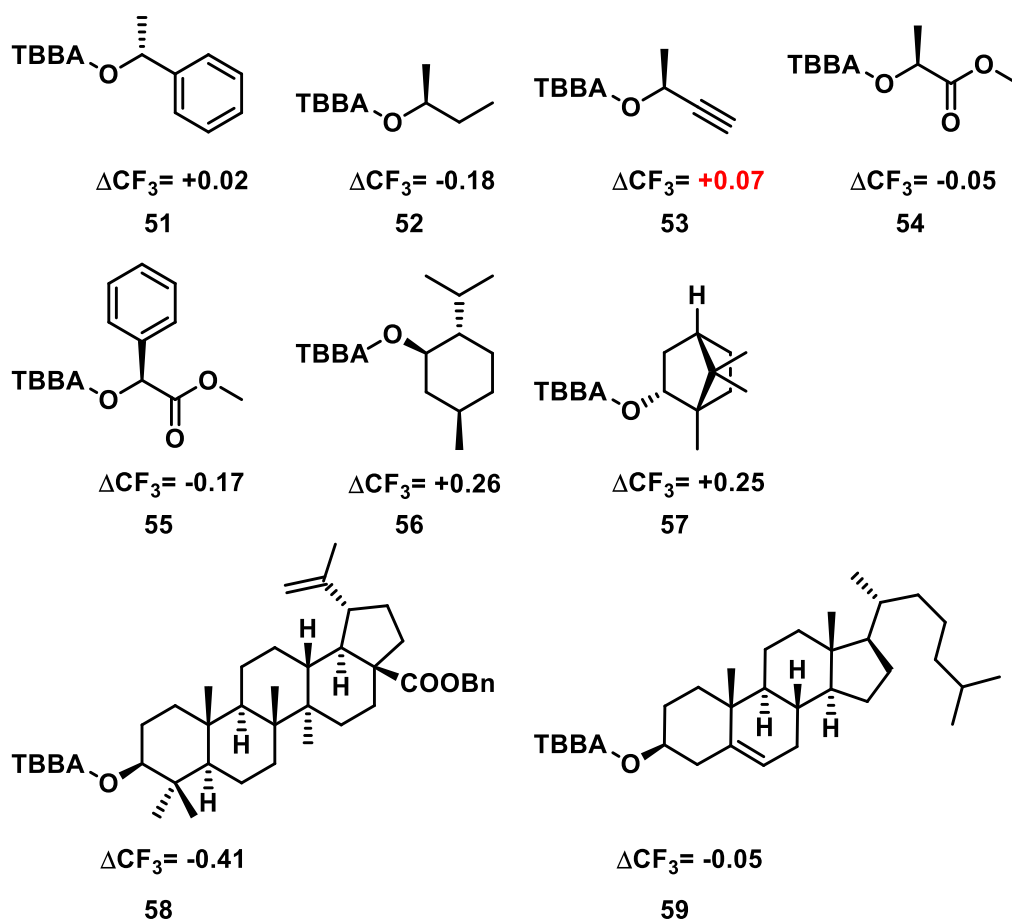


Figure 14 observed ΔCF_3 for esters **51-59**

Menthol **56** and borneol **57** displayed very similar ΔCF_3 +0.26 and +0.25 ppm, respectively, which were higher compared to esters **51-55** and comparable to most of the analyzed amides. The two terpene derivatives **58** and **59**, although similar in structure, displayed a highly dissimilar ΔCF_3 : -0.41 for **58** and -0.05 for **59**. To our delight, compounds **51-59** displayed homogenous sign distribution of the ΔCF_3 differences apart from the compound **53**. The simple model was proposed in **Figure 15**.

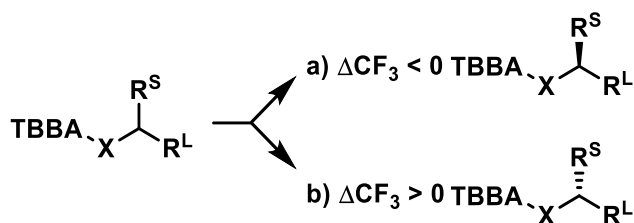


Figure 15 First proposed model for observed ΔCF_3

Assuming the large substituent (R^L) is positioned in the plane, the small substituent is positioned in front of the plane if the $\Delta CF_3 < 0$ (**Figure 15a**) and vice versa, if the $\Delta CF_3 > 0$, then the small substituent is positioned behind the plane (**Figure 15b**). Unfortunately, this simplification only reliably works for acyclic compounds. In the case of cyclic esters **56-59** the large substituent R^L is clearly identified. The approximate size-priority of substituents is from R^L to R^S : *tert*-butyl > ester > aryl > isopropyl > benzyl > hydroxymethylene > methyl.

The difference in the ^{19}F spectra is likely caused by shielding or deshielding of the trifluoromethyl group by the substituents L^1 and L^2 of the analyte. The shielding cones are displayed in **Figure 16**.^{163,164}

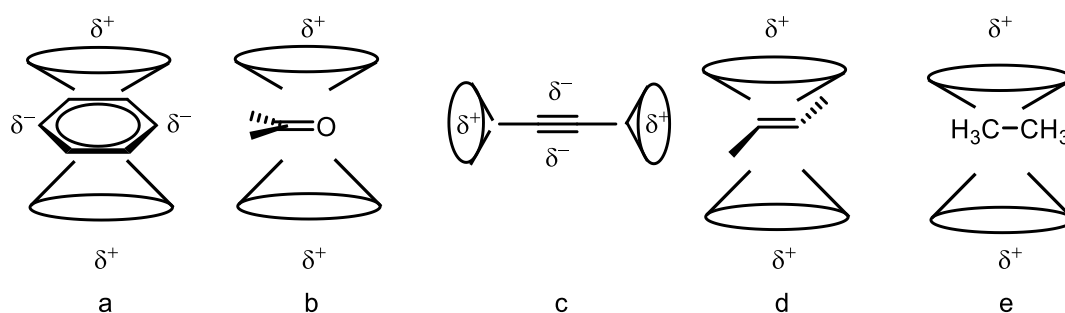


Figure 16: shielding cones a) aryl b) carbonyl group c) alkyne d) alkene e) alkane

δ^+ : shielding δ^- : deshielding

Those shielding effects projected by substituents shield or deshield the CF_3 group (**Figure 17**) and then, it is observed as a difference of the ^{19}F chemical shifts (**Figure 13** and **14**).

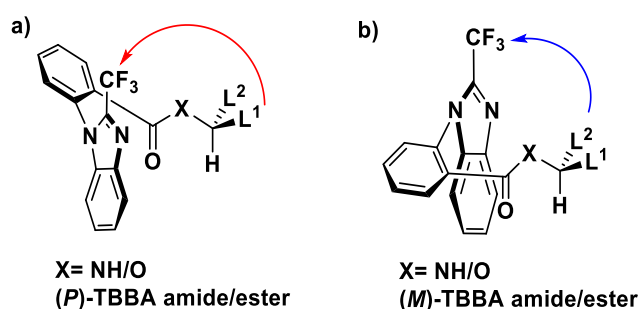


Figure 17 Possible explanation for the observed ΔCF_3 differences

This model explains the observed differences in the ^{19}F spectra and, furthermore, reveals the origin of the anomalous value for alkyne **53**, where the anisotropic effect of the alkyne is different. This difference is displayed in **Figure 18**, where the shielding effects of amide (**P**)-**40** and ester (**P**)-**53** are compared.

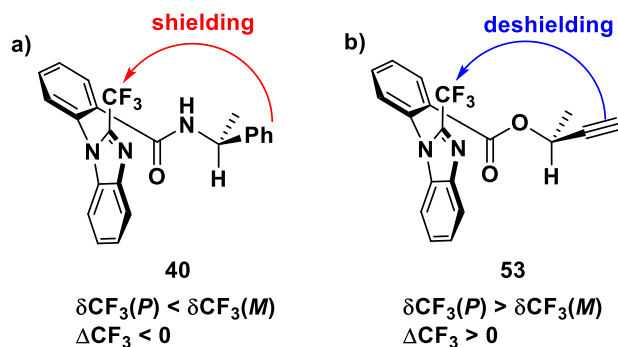


Figure 18 Possible explanation for the observed ΔCF_3 values of compounds **40** and **53**

As can be seen in **Figure 18**, the same arrangement of the substituents in space causes the different chemical shifts of ^{19}F spectrum. The phenyl ring causes shielding of the CF_3 group in the (**P**)-**40**, and it resonates upfield. For this reason, a lower chemical shift was observed compared to the (**M**)-**40** and, as a result, the negative ΔCF_3 was obtained after the subtraction. The alkyne moiety in (**P**)-**53**, although located at the same position in space as the phenyl ring in (**P**)-**40**, causes deshielding of the CF_3 group. Then the higher chemical shift is observed, therefore a positive ΔCF_3 is obtained.

Since the simple alkyl group projects the shielding effect as well,^{164,165} the observed ΔCF_3 in aliphatic derivatives **42**, **46**, **47**, **52**, **56-59** can be also explained. Our explanation is based on the hypothesis that the branched or longer aliphatic chains project stronger shielding effect compared to unbranched or shorter chains. The lack of branching or multiple bonds on the A-ring of the cholesterol derivative is the likely cause of the low observed ΔCF_3 (-0.05).

In the end, the use of ^{19}F NMR is more complicated than 1H or ^{13}C NMR because the observed ΔCF_3 values depend not only on the absolute configuration of the analyte but also on the identity of the present functional groups. Furthermore, only one data point is obtained for each diastereomer, therefore, their comparisons always yield configuration with no space for self-correction. This is not the case of 1H or ^{13}C analysis where multiple signals could be analyzed and any anomalous data can be resolved. This was shown in the case of MTPA which displayed lower than 50% reliability when using ^{19}F spectra.⁸⁶

3.5.2. Analysis of β -chiral alcohols and amines

After the analysis of α -chiral compounds was finished, we turned our attention towards more complex β -chiral compounds. The analysis of this type of compounds is more complicated due to following reasons:^{69,71,92,166}

- Additional carbon in the structure highly increases the conformational flexibility; therefore, the NMR relevant conformer is less prevalent compared to α -chiral compounds.
- The chiral center is located further away from the group projecting the anisotropic shielding effect.

For those reasons, the observed $\Delta\delta^{RS}$ values are smaller compared to the α -chiral derivatives and the only CDA that can produce sufficient and reliable differentiation is 9-AMAA. While MPA or MTPA work in some cases, the differentiation is significantly smaller compared to 9-AMAA and in some cases no differences in chemical shifts are observed.^{69,71}

The advantage of TBBA compared to MPA or MTPA lies in lower conformational flexibility, which should allow more selective projection of the anisotropic shielding effect. Furthermore, the size of the benzimidazole ring is approximately in the middle between phenyl and anthryl rings of MPA/MTPA and 9-AMAA. The library of 18 esters (**Figure 19**) was prepared with the alcohols chosen to match the already prepared 9-AMAA esters to allow direct comparison of TBBA and 9-AMAA.^{69,71} The analysis was conducted in the same manner as for the α -chiral alcohols and amines.

3.5.2.1. ¹H NMR analysis

At first, (*S*)-2-methylbutan-1-ol **60** (**Figure 19**) was used as the simplest alcohol available. The methyl group displayed $\Delta\delta^{PM}$ -0.11 ppm for the methyl group and +0.06 ppm for the ethyl group. Those values were comparable to the 9-AMAA which yielded a lower difference (-0.01 ppm) on the methyl group but slightly higher (+0.08 ppm) for the ethyl group. The observed differences were significantly higher than those of MPA (+0.02, -0.01) and MTPA (+0.00 and -0.01) esters.⁷¹

Substitution of the ethyl group for bromomethylene in **61** did not have significant effect and yielded high $\Delta\delta^{PM}$ for ester **53**. The observed differences, -0.12 for methyl and +0.23 for methylene, were similar to the 9-AMAA with the difference at the methylene protons being higher (+0.23 vs +0.09). Further substitution of the bromide for the carboxymethyl group in **62** displayed similar $\Delta\delta^{PM}$ on the methyl group (-0.11). This difference was very similar to **60** and **61** and very close to the 9-AMAA (+0.1). As expected, the more remote carboxymethyl group showed lower $\Delta\delta^{PM}$ of +0.06 which was slightly lower

than 9-AMAA (+0.1). In comparison to those of MTPA (-0.01 and +0.01) and MPA (+0.02 and -0.04), the TBBA $\Delta\delta^{PM}$ values were significantly higher.⁷¹

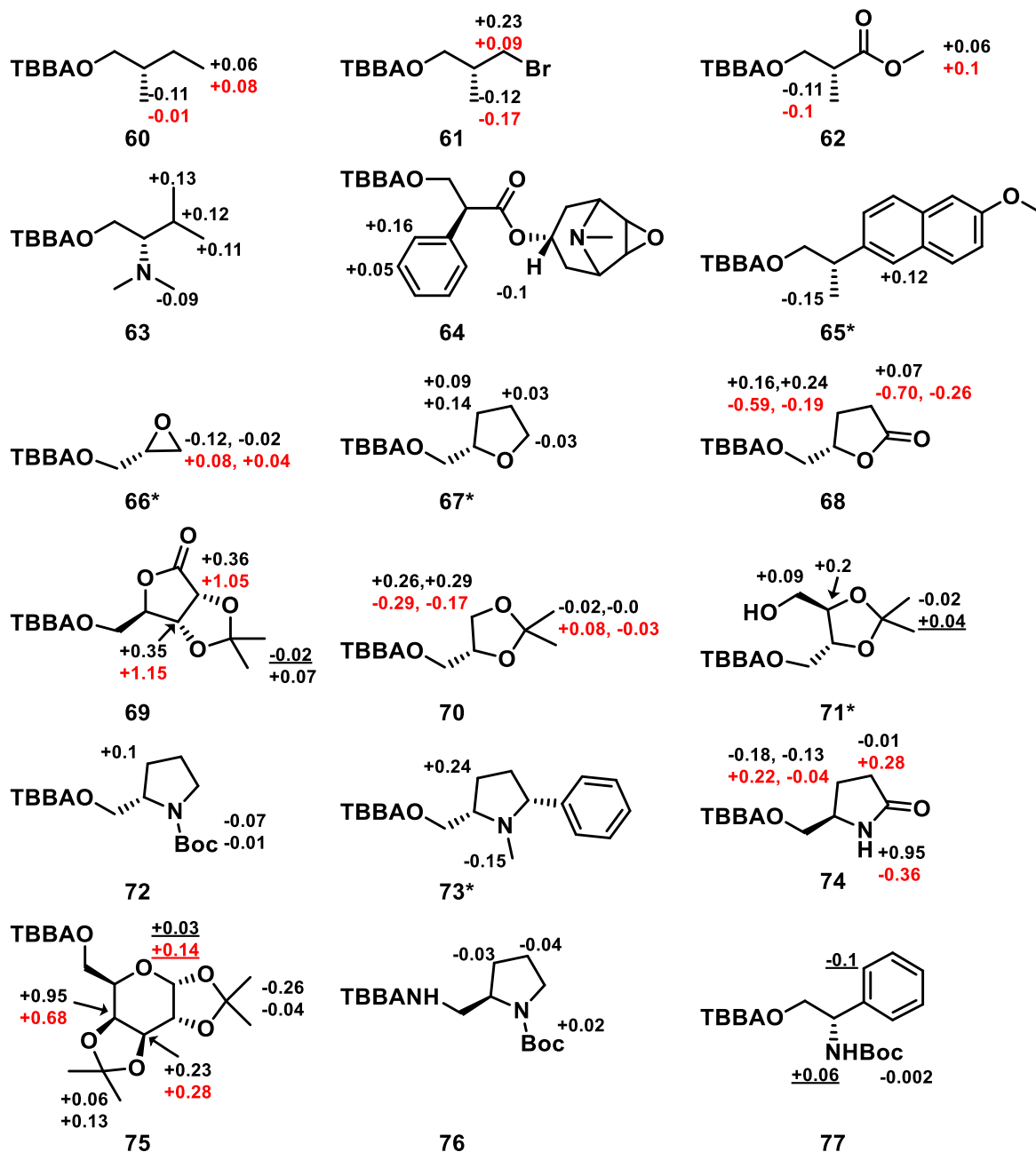


Figure 19 Observed $\Delta\delta^{PM}$ for compounds 60-77, black: TBBA, red: 9-AMAA, anomalous values are underlined.

*Compound was prepared by undergraduate student David Profous.

** 9-AMAA esters **66**, **70**, **64** were prepared from the starting materials with opposite absolute configuration compared to TBBA esters. Therefore, the sign of the $\Delta\delta^{RS}$ is opposite compared to TBBA.

Branched alkyl chain in **63** slightly increased the observed $\Delta\delta^{PM}$ of the isopropyl group (+0.11, +0.12 and +0.13) compared to the unbranched ethyl in **60**. The difference of the dimethylamino group was slightly lower as expected due to the methyl groups being located further away from the chiral center compared to the methyl group in **60**, **61**, and **62**. It was reported that the presence of polar groups can change the conformation equilibrium,⁹² it does not seem to be the case of compounds **62** and **63**. The observed $\Delta\delta^{PM}$ values are fairly high and distortion of the conformations was expected to significantly lower the observed $\Delta\delta^{PM}$.

Aromatic derivatives **64** and **65** were tested as well. In the case of **64**, partial (approx. 10%) racemization was observed during the preparation of the ester, nevertheless it still allowed for NMR analysis. Protons in the *ortho* position of the phenyl ring displayed +0.16 ppm difference while the protons at the *meta* position displayed lower +0.05 ppm difference. The proton in the scopolamine moiety displayed $\Delta\delta^{PM}$ of -0.1 ppm which is comparable to the methyl ester **62**. Naproxol **65** showed -0.15 ppm difference at the methyl group and +0.12 at the *ortho* position, which is comparable to scopolamine derivative **64** and methyl substituted compounds **60-62**. The $\Delta\delta^{PM}$ values of (*S*)-glycidol TBBA ester **66** (-0.12 and -0.02 ppm) were comparable to those of the 9-AMMA ester, although a different conformational model was used with the 9-AMAA ester.⁹² While only one substituent was analyzed for **66**, the +0.2 ppm difference at position 2 suggested that a similar modification of the conformational model could be applied in the case of TBBA.

The $\Delta\delta^{PM}$ differences of tetrahydrofuran **67** at position 3 were +0.09 and +0.14 ppm and further decreased at positions 4 (+0.03 ppm) and 5 (-0.03 ppm). Tetrahydrofuranone **68** showed smaller $\Delta\delta^{PM}$ differences (+0.24 and +0.07 ppm) compared to those of the 9-AMAA ester (-0.59 and -0.7 ppm) and slightly higher differences compared to those of **67**. This was evidently caused by the presence of the carbonyl group which alters the bond angles in the furanone ring. Ribonic- γ -lactone **69** displayed +0.36 and +0.35 ppm differences at the most relevant positions (smaller differences compared to those of the 9-AMAA ester)⁷¹, and one of the acetonic methyl groups showed an anomalous negative sign. However, the magnitude of this difference was small and thus it can be ignored.

The $\Delta\delta^{PM}$ values of the methylene group in glycerol **70** were +0.26 and +0.29 ppm for TBBA but only -0.05 and -0.07 for MPA and -0.01 and -0.03 ppm for MTPA. The values of the 9-AMAA ester (-0.29 and -0.17 ppm)⁷¹ were similar to those of TBBA. Tartaric acid derivative **71** showed $\Delta\delta^{PM}$ values of +0.2 and +0.09 ppm. The difference of the CH proton was comparable to those of protons at the same positions in **67**, **68** and **69**.

The protons at the position 3 of boc-prolinol **72** displayed a difference of +0.1 ppm. Two values of -0.07 and -0.01 ppm of $\Delta\delta^{PM}$ were observed for the Boc group due to signal splitting into two singlets corresponding to 3 and 6 protons in the case of the diastereomer (*P*)-**72**. The splitting was not observed in the case of (*M*)-**72**. This phenomenon was likely caused by the partial presence (on average) of one

methyl group slightly outside of the shielding cone. The $\Delta\delta^{PM}$ values of **72** were slightly lower than those of other ring structures, such as **67-71**.

Interestingly, the *N*-methylprolinol derivative **73** showed a significantly higher $\Delta\delta^{PM}$ compared to the *N*-boc derivative **72**. As expected, the $\Delta\delta^{PM}$ of the methyl group is higher compared to the boc because the protons are closer to the chiral center and therefore located more inside the shielding cone compared to the boc group. Interestingly, the $\Delta\delta^{PM}$ at the position 3 is more than double of the in the boc-derivative **72**. The pyroglutaminol ester **74** showed significant $\Delta\delta^{PM}$ at the position 1 (+0.95) which is higher in magnitude than 9-AMAA (-0.35). The differences at position 3 (-0.18 and -0.13) were similar to the 9-AMAA (+0.22 and anomalous +0.04) while the difference at position 4 was significantly smaller (-0.01 vs +0.28).

The protected galactopyranose ester **75** showed high $\Delta\delta^{PM}$ of +0.95 ppm at position 5 and +0.23 ppm at position 4, which were comparable to those of the 9-AMAA ester (+0.68 and +0.28 ppm).¹⁸ Unfortunately, the anomalous $\Delta\delta^{PM}$ value at position 2, as was also observed for the 9-AMAA ester, could slightly complicated the assignment. Nevertheless, the small anomalous value of the TBBA ester at position 2 could be ignored since the most relevant signals displayed correct values.²⁴

Generally, acetonide methyls were variously located in or out of the shielding zone. Thus, the sign distribution of the galactopyranoside acetonide methyl groups in **75** showed major differences in $\Delta\delta^{PM}$ values (-0.04, -0.26, +0.06 and +0.13) for the acetonide methyls, unlike derivatives **69**, **70**, and **71**. Like **69**, one of the acetonide methyl groups of **70** showed an anomalous positive $\Delta\delta^{PM}$ value, whereas **70** did not. However, one of the methyls in **70** showed a $\Delta\delta^{PM}$ value close to zero.

To preliminarily prove whether the method can be extended to β -chiral primary amines, amide **76** was prepared and compared with ester **72**. Boc-pyrrolidine **76** showed significantly smaller $\Delta\delta^{PM}$ differences at the relevant protons (-0.03, -0.04, and +0.02) than those of **72**, **73**, and **74**. The smaller $\Delta\delta^{PM}$ values observed for compounds **72** and **76** were likely caused by the large boc protecting group. As expected, the $\Delta\delta^{PM}$ of *N*-substituents decreased with increasing distance from the nitrogen atom (+0.95 ppm for **74**, -0.15 for **73**, and -0.01 and -0.07 ppm for **72**).

Interestingly, (*S*)-Boc-Phenylglycinol **77** was not in accordance with the proposed model, and the opposite configuration was observed. This limitation of the method was likely caused by the sterically demanding Boc group, which impacted the conformational equilibrium. This seemed to agree with the low $\Delta\delta^{PM}$ values for boc-substituted derivatives **72** and **76**.

3.5.2.2. Conformational model for assignment of absolute configuration by ¹H or ³C NMR

Based on the experimental data, conformational model (**Figure 20**) for assignment of the absolute configuration was proposed. At first, the proton at the chiral center (C α) is in *anti*-periplanar conformation to the carbonyl group. This allows the benzimidazole to project the shielding effect

towards the L² substituent (**Figure 20a**). Naturally, in the (*M*)-diastereomer (**Figure 20b**), the shielding effect is produced towards the substituent L¹. Analogously to the α-chiral compounds, the Δδ^{PM} parameter is calculated following the equation in **Figure 20c**. The simplified model is shown in **Figure 20d**: if the substituent has Δδ^{PM} less than zero, it is located above of the carbonyl-Cα plane while if the Δδ^{PM} is higher than zero, the substituent is located under the plane.

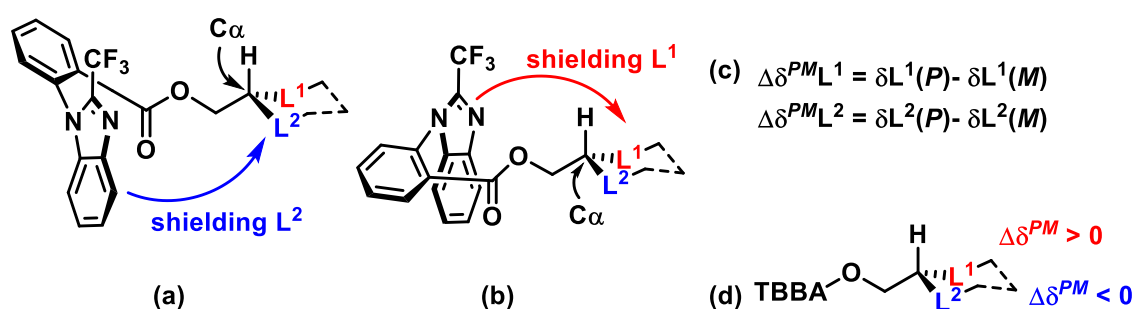
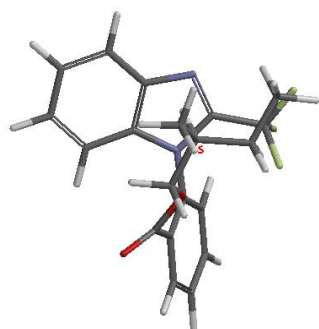


Figure 20 Conformational model for the assignment of the absolute configuration of chiral primary alcohols a) (*P*)-TBBA ester b) (*M*)-TBBA ester c) calculation of Δδ^{PM} d) simplified model.

To further strengthen the proposed model, DFT calculations were performed using Spartan 16 software using ester **60** as the model compound. The populations of theoretical conformers were calculated with the molecular mechanics model MMFF. Depending on the total number of theoretical conformers, this was followed by sorting of the conformation candidates with relative energies lower than 10–20 kJ/mol. The energies of sorted candidates at the ground state in the nonpolar solvent were calculated using density functional theory (B3LYP, 6-31G*) to find the lowest energy conformer.

a)

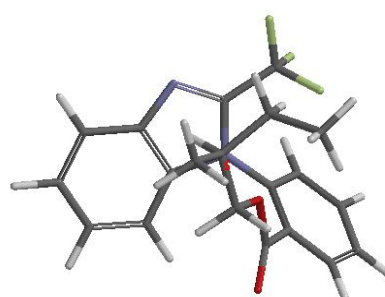


Most stable conformer

NMR relevant conformer

(0.358)

b)

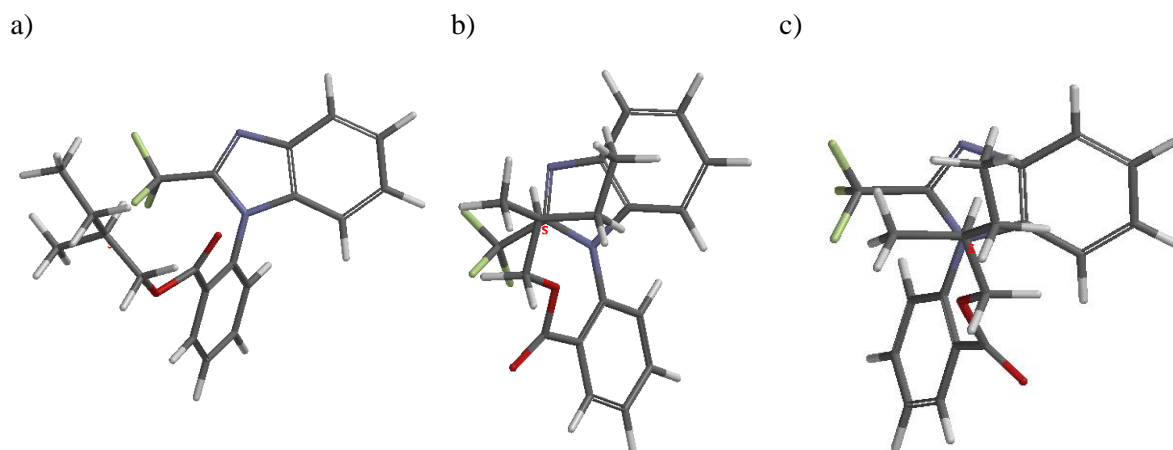


2nd most stable conformer

NMR-relevant

(0.091) ΔG= 3.39 kJ/mol

Figure 21 Conformers of (*P*)-**60**



Most stable conformer	2nd most stable conformer	3rd most stable conformer
NMR irrelevant conformer	NMR relevant conformer	NMR relevant conformer
(0.173)	(0.163) $\Delta G = 0.12$ kJ/mol	(0.092) $\Delta G = 1.56$ kJ/mol

Figure 22 Conformers of (*M*)-60

As expected, the number of conformers is higher compared to α -chiral alcohols or amines. The most relevant conformers for diastereomer (*P*)-60 are shown in **Figure 21**. The most stable conformer (Boltzmann weight 0.358) is shown in **Figure 21a**. The proton at $C\alpha$ is in *anti*-periplanar position to the carbonyl group which allows the methyl group to be shielded by the benzimidazole ring. The *anti*-periplanar conformation is slightly distorted and the $C\alpha$ proton is also partially located in the shielding zone of the benzimidazole. The second most stable conformer with Boltzmann weight 0.091 (**Figure 21b**) has the methyl and ethyl substituents located in a same manner as the most stable conformer. The difference is caused by the rotation of the ethyl group.

In the case of (*M*)-60 diastereomer the conformation equilibrium is more complex since the most abundant conformer (**Figure 22a**) with Boltzmann weight 0.173 is not NMR relevant. None of the substituents of the alcohol are outside of the shielding zone. The second most stable conformer (Boltzmann weight 0.162 kJ/mol) is the most NMR relevant although the conformation is different compared to the described model (**Figure 22b**). The proton at $C\alpha$ is rotated approximately 60° from the *anti*-periplanar conformation to the carbonyl group which moves the methyl group to the *syn*-periplanar conformation with the carbonyl group. Nevertheless, the ethyl group remains in the shielding zone of the benzimidazole. This conformational changes were already described by Seco⁹² for compounds possessing polar groups such as methoxy or boc-amino (**Figure 23**). Further 60° rotation around the $C\alpha$ - CH_2CO bond leads to the third most stable conformer of the diastereomer (*M*)-60 which is also NMR-relevant with the ethyl group being located inside the shielding zone of the benzimidazole (**Figure 22c**).



Figure 23: Model conformation of β -chiral 9-AMAA esters a) normal conformation b) preferred conformation if bulky and/or polar group is present (Pg= bulky/polar group)⁹²

3.5.2.3. Investigation of the Boc-protected amino alcohols

At first, a small library of Boc-protected amino alcohols was synthesized to confirm, if the unexpected conformations of compound **77** are only an anomaly or if there is an ongoing trend (**Figure 24**)

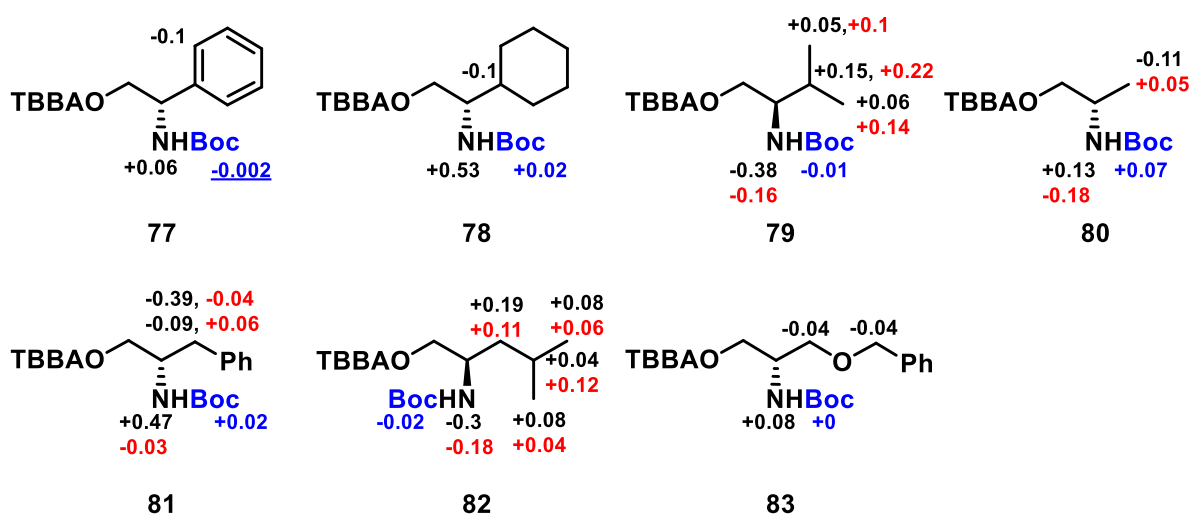


Figure 24 Analyzed boc-amino alcohols and their $\Delta\delta^{PM}$ values. Underlined values follow the previously proposed model. 9-AMAA values⁷¹ are shown in red. 9-AMMA esters **79** and **82** were prepared from alcohol with opposite configuration compared to TBBA ester. $\Delta\delta^{PM}$ of the boc group is displayed in blue for higher clarity

As described above, the (*S*)-boc-phenylglycinol ester **77** displayed -0.1 ppm difference at the *ortho* position of the phenyl ring and +0.06 of the NH. Using those values and the previously described model (**Figure 20**) yielded opposite configuration. The protons in the *tert*-butyl moiety in the boc protecting group displayed $\Delta\delta^{PM}$ of -0.002 which is in the agreement with the proposed model, but the difference is on the edge of the limitations of the NMR measurements.

Boc-cyclohexylglycinol **78** showed reliable distribution of $\Delta\delta^{PM}$: +0.53 for NH, +0.02 for boc and -0.1 ppm for the proton at position 1 but when those values were used for the configuration assignment, opposite than expected configuration was obtained as in the case of phenylglycinol **77**.

Reduction of the size of the substituent by substitution of the cyclohexyl ring for isopropyl in **79** had only a minor effect on the observed $\Delta\delta^{PM}$ values. The NH proton displayed -0.38 ppm which is higher

compared to the 9-AMAA derivative ($\Delta\delta^{RS}$ -0.16). The boc protons displayed higher $\Delta\delta^{PM}$ (-0.01) compared to **79** and slightly smaller compared to **77**. The observed differences of the isopropyl moiety (+0.05, +0.15 and +0.06) were slightly smaller compared to 9-AMAA derivative (+0.1, +0.22 and +0.14).^{71,92} The Boc-aminopropanol **80** showed lower $\Delta\delta^{PM}$ compared to **78** or **79**. The methyl group displayed -0.11 ppm difference which is higher compared to the 9-AMAA ester (0.05) while the observed $\Delta\delta^{PM}$ of the boc-amino group were slightly lower (+0.13 for TBBA and -0.18 for 9-AMAA).⁷¹

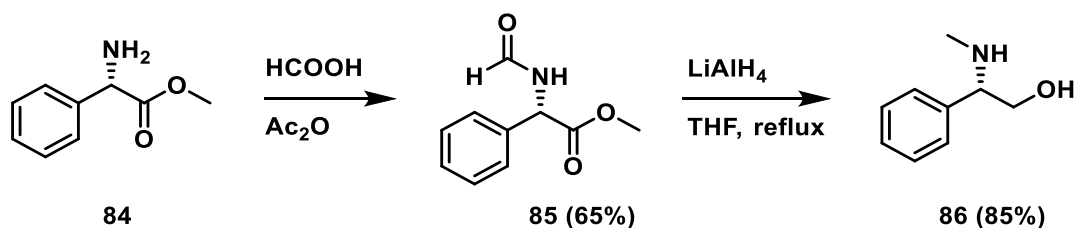
Further modification of the structure by the addition of the phenyl ring in phenylalaninol **81** displayed high $\Delta\delta^{PM}$ +0.47 for the amino group which is significantly higher than the 9-AMAA ester (-0.03). The protons at the benzylic position displayed -0.39 and -0.09 ppm difference. Interestingly, the 9-AMAA ester displayed an anomalous value of one of the protons at the benzylic position. Substitution of the phenyl ring for isopropyl in **82** caused a significant change of the observed $\Delta\delta^{PM}$ values compared to the phenylalanine derivative **81**. The amino group displayed -0.3 ppm difference which is smaller compared to derivatives **78**, **79**, and **81**. The proton in *tert*-butyl group displayed -0.02 ppm difference which is in the same magnitude compared to previously described boc-amino alcohols **78-81**. Compared to 9-AMAA, compound **82** showed differences of a roughly same magnitude.

Last, the introduction of the more polar benzyl ether group of boc-benzylserinol derivative **83** caused an interesting drop of observed $\Delta\delta^{PM}$ values. No $\Delta\delta^{PM}$ was observed in the case of boc group, while the NH proton displayed +0.08 ppm which is comparable to phenylglycinol derivative **77**. The protons at the benzyl and at position 3 displayed small -0.04 ppm differences. The exact cause of this small differences is unknown but possibly the preference for specific conformers is low in compound **83** due to the similar sizes of Boc-amino group and the benzyl ether moiety.

3.5.2.4 Analysis of phenylglycinol derivatives

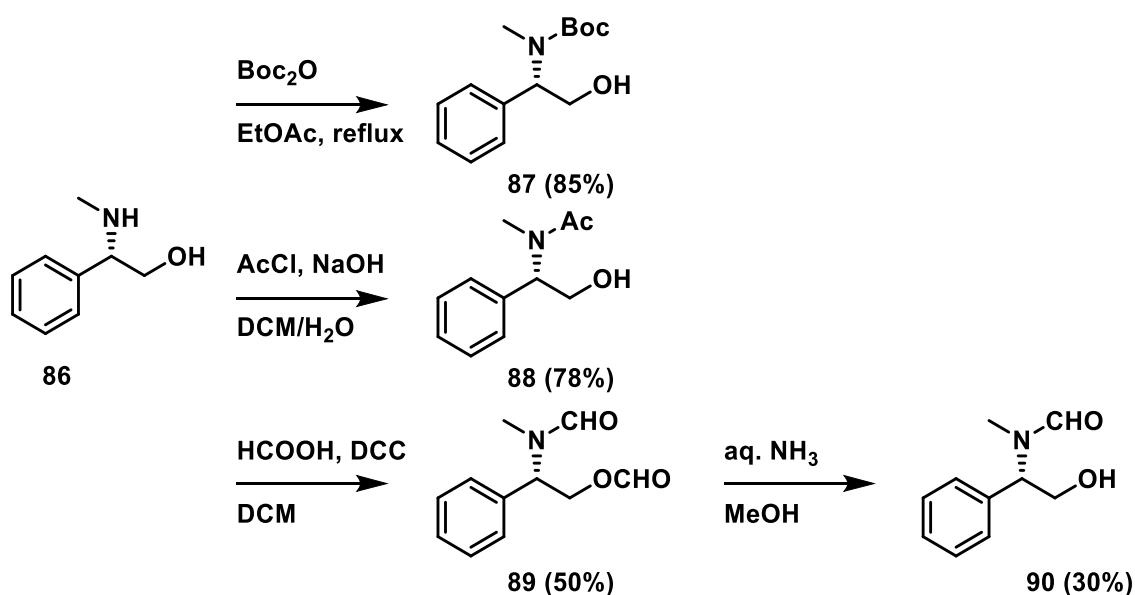
Because the boc-protected amino alcohols clearly displayed a preference for different conformation states compared to the previously developed model for β -chiral alcohols, the library was further expanded with various *N*-substituted phenylglycinols to further investigate the conformational model. At first, the *N*-methyl phenylglycinol derivatives were prepared to investigate the presence of the hydrogen bond.

Various methods to prepare key *N*-methylphenylglycinol **86** such as direct methylation of phenylglycinol with MeI, direct methylation of *N*-boc-phenylglycinol with MeI; however, they did not yield any product at all. LiAlH₄ reduction of *N*-carbamates did not provide any product although the method was reported multiple times in the literature.^{167,168} For this reason, a multistep sequence was used (**Scheme 14**).^{169,170}



Scheme 14 Synthesis of *N*-methyl phenylglycinol

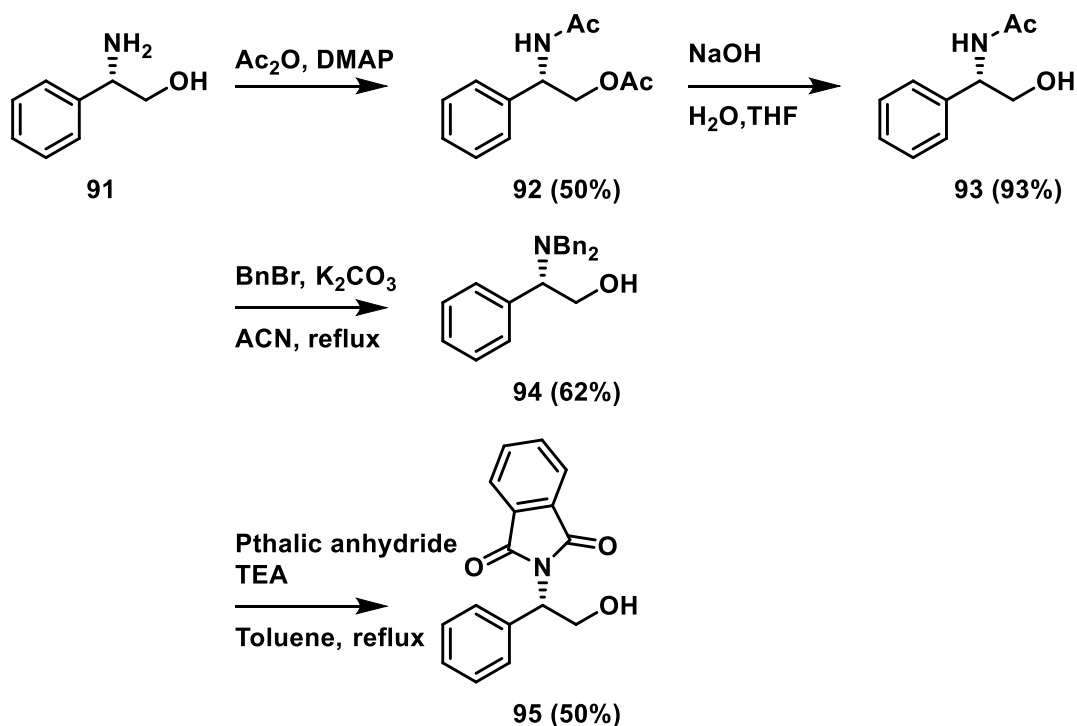
Starting from phenylglycine methyl ester **84** which was formylated using Ac_2O and HCOOH in 65% yield. Compound **85** was then reduced using LiAlH_4 in refluxing THF in high yield (85%).¹⁷¹ Intermediate **86** was then converted into various *N*-methylphenylglycinols (**Scheme 15**).



Scheme 15 Synthesis of *N*-methyl phenylglycinol derivatives

Boc-protection using Boc_2O in refluxing ethyl acetate yielded derivative **87**.¹⁷¹ Acylation of **86** with acetyl chloride in biphasic system $\text{DCM}:\text{H}_2\text{O}$ yielded acetylated derivative **88**, which was isolated as a mixture of amidic rotamers in 10:4 ratio.¹⁷² Formylation with already used $\text{Ac}_2\text{O}+\text{HCOOH}$ system yielded a complex mixture of products. Luckily, HCOOH and DCC ¹⁷³ yielded product **89**. Although the mono-formylated compound **90** was observed on TLC, the conversion of **86** to **89** was very fast and **90** was impossible to isolate from the reaction mixture in useful yields. Therefore, the reaction was left to completion and compound **89** was isolated with the idea of subsequent ester hydrolysis in the separate step. Hydrolysis of **89** using aq. NaOH yielded complex mixture of products. The use of the aq. ammonia solution fully hydrolyzed the ester while keeping the amide bond intact. As in the case of **88**, compounds **89** and **90** were isolated as amidic bond rotamers.

N-acetyl phenylglycinol **93** was prepared in a similar manner as formyl derivative **90** by hydrolysis of the ester **92**.¹⁷⁴ Dibenzyl **94**¹⁷⁵ and phthalimide **95**¹⁷⁶ protected phenylglycinols were prepared according to the literature procedures (**Scheme 16**).



Scheme 16 Synthesis of phenylglycinol derivatives

With the protected alcohols **87**, **88**, **90**, **93-95** in hand, the library of TBBA esters was expanded (**Figure 25**). The *N*-Methyl-*N*-Boc derivative **96** displayed +0.1 ppm difference at the methyl group while -0.01 ppm at the Boc and *ortho*-protons. The observed $\Delta\delta^{PM}$ was smaller compared to the non-methylated compound **77**. Importantly, the configuration obtained using the $\Delta\delta^{PM}$ for compound **96** was opposite as in the case of compound **77**. The dimethyl derivative **97**, showed -0.1 ppm difference for the dimethylamino group and +0.08 and +0.03 for *ortho* and *meta* protons on the phenyl ring. The obtained configuration was correct which was expected due to the structural similarity to compound **63** (**Figure 19**). This observation revealed no significant effect of the phenyl ring on the conformations as was reported in literature.¹⁵⁷

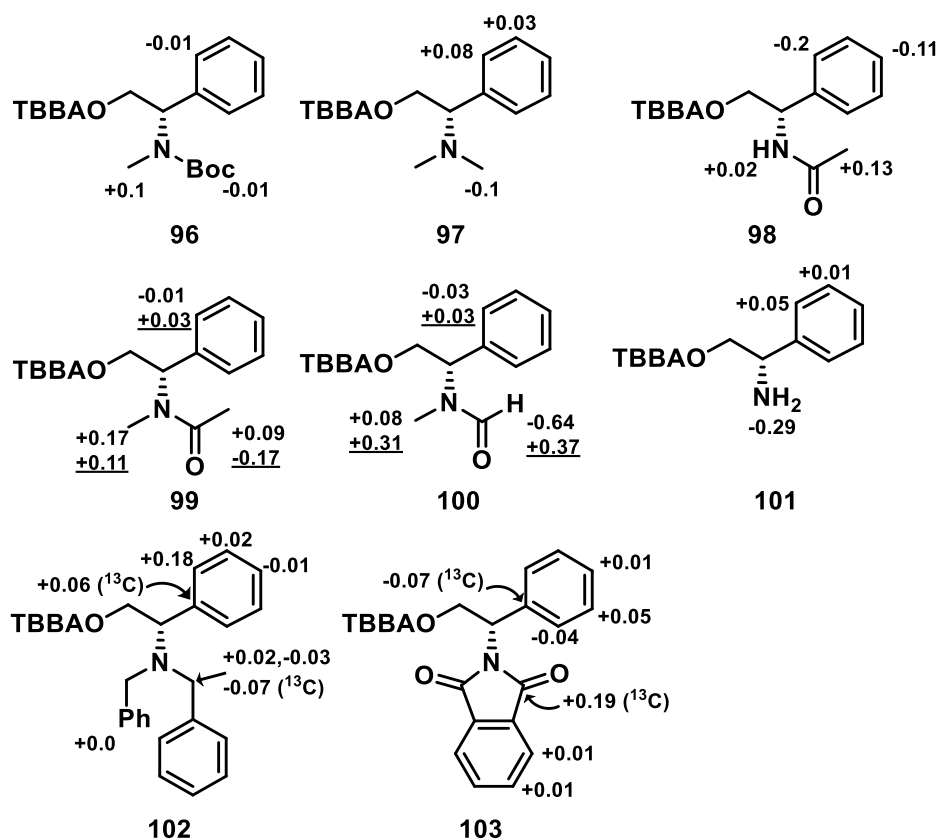


Figure 25 Observed $\Delta\delta^{PM}$ in derivatives **96-103**, minor rotamers are underlined

N-acetyl ester **98** showed +0.13 and +0.02 $\Delta\delta^{PM}$ at the acetyl group and amide proton respectively. The phenyl ring displayed -0.2 ppm difference at the *ortho*-position and -0.11 ppm at the *meta* and *para* positions and again. The magnitude of observed $\Delta\delta^{PM}$ in **98** was comparable to alcohols **60-83** (**Figures 19** and **24**). Based on the calculated $\Delta\delta^{PM}$ values the opposite configuration was obtained as in the case of compounds **77-83** and **96**. This further suggests the hydrogen bond plays an effect, although it is not the sole reason for the preference of a different conformer since the *N*-methyl derivative **96** also yielded opposite configuration.

The *N*-methylation had a significant effect on the observed $\Delta\delta^{PM}$. First, ester **99** was isolated as a mixture of amide bond rotamers as was parent alcohol **88** which complicated the analysis. The major rotamer showed +0.17 and +0.09 $\Delta\delta^{PM}$ for both methyl and acetyl protons while the phenyl displayed small -0.01 ppm difference at the *ortho* position. The minor rotamer showed +0.11 and -0.17 ppm for the methyl and acetyl protons and +0.03 ppm for the proton the *ortho* position of the phenyl ring. Using the observed $\Delta\delta^{PM}$ values for the configuration assignment, one can see that the major rotamer yields the opposite configuration while the minor rotamer gives ambiguous results.

Substitution of the acetyl for sterically less demanding formyl in the ester **100** showed similar results as the acetamide **99**. The product was again isolated as a mixture of two rotamers. The major rotamer

displayed unusually high $\Delta\delta^{PM}$ of the formyl group: -0.64 ppm. The methyl group showed $\Delta\delta^{PM}$: +0.08 ppm and the proton in ortho position of the phenyl ring displayed -0.03 ppm difference. Although the formyl group displayed high $\Delta\delta^{PM}$, the remaining two protons (methyl and ortho-Ph) showing anomalous sign of their $\Delta\delta^{PM}$ make the correct assignment inconclusive. The minor rotamer displayed +0.31 and +0.37 ppm for the methyl and formyl group, respectively, while the proton at the *ortho* position of the phenyl ring showed +0.03 ppm difference. This anomalous value again makes the configuration assignment inconclusive.

The *N*-unprotected ester **101** was prepared by the removal of the boc-group from compound **77** using 20% TFA in dichloromethane. The removal of the protecting group had a significant effect on the observed $\Delta\delta^{PM}$ values. The unprotected amino group displayed -0.29 ppm while the *ortho* and *para* protons displayed +0.05 and +0.01 ppm respectively. Those observed $\Delta\delta^{PM}$ values matched the previously developed conformational model as in the case of the dimethyl derivative **97** and correct configuration was obtained.

Furthermore, dibenzyl **102** and phthalimide **103** protected phenylglycinols were prepared as well. Those two groups could be used as the ammonia equivalents^{177,178} and for this reason, the analysis of those derivatives is of high interest. The dibenzyl derivative **102** displayed positive $\Delta\delta^{PM}$ values on the phenyl ring: +0.18 ppm for the *ortho* proton, +0.02 ppm for the *meta* proton and anomalous -0.01 ppm for the proton in the most remote *para* position. The dibenzyl group showed 0 ppm difference in the aromatic rings while both positive (+0.02) and negative (-0.03) $\Delta\delta^{PM}$ values at the benzylic position. Although the anomalous value in the *para* position of the phenyl ring could be ignored, as being low in magnitude and far away from the chiral center, this logic cannot be applied in the case of the benzylic protons. Both $\Delta\delta^{PM}$ values at the benzylic position are similar in the absolute magnitude and the protons are located directly adjacent to the chiral center. Because of this discrepancy the ¹³C NMR spectra were analyzed as well. The quaternary carbon in the phenyl ring displayed $\Delta\delta^{PM}$ of +0.06 ppm while the carbon at the benzylic position displayed difference of -0.07 ppm. Combining ¹H and ¹³C NMR data and the conformational model developed for the β -chiral compounds, then the correct configuration was obtained.

The phthalimide derivative **103** displayed similar behavior. The protons in phthalimide moiety displayed +0.01 ppm difference while the protons in the phenyl ring showed anomalous behavior: the $\Delta\delta^{PM}$ for the protons in the *ortho* position was -0.04 ppm while the *meta* and *para* protons showed positive +0.05 and +0.01 $\Delta\delta^{PM}$. As in the case of **102**, ¹³C NMR was analyzed to resolve the observed anomalous $\Delta\delta^{PM}$ values. The ¹³C NMR showed +0.19 ppm difference for the carbonyl carbons and -0.07 ppm for the quaternary carbon in the phenyl ring. Using those values and the previously developed model, the incorrect absolute configuration is obtained for the phthalimide **103**.

3.5.2.5. ^{19}F NMR analysis of β -chiral alcohols and amines

^{19}F NMR spectra were analyzed as well (**Figure 26**) to see whether a suitable model might be developed. At first, compounds **60-77** were analyzed because they followed the proposed model for β -chiral compounds (except for compound **77**). Similar assumptions were made about shielding cones (**Figure 16**) as in the case of α -chiral derivatives. In general, approximately a half of the compounds followed the general model and display ΔCF_3 differences between 0-0.6 ppm.

The valinol derivative **63** displayed 0 ppm difference between the (*P*)- and (*M*)- diastereomer, likely due to the similarities between the isopropyl group and dimethylamino group. Scopolamine ester **64** displayed a negative ΔCF_3 value. This suggests that the carbonyl group produces a stronger shielding effect compared to the phenyl ring. Furthermore, the phenyl ring might be oriented in a way that projects the deshielding effect towards the CF_3 group. Similar anomalous ΔCF_3 is observed in the case of naproxol ester **65** which should project shielding effect on the CF_3 group in the (*M*)-diastereomer to yield a positive ΔCF_3 difference; however, a negative difference was observed. Ester **66** also displays anomalous ΔCF_3 with the expected shielding coming from CH_2 group is projected towards the trifluoromethyl group in the (*M*)- instead of (*P*)-diastereomer. Likely, the small size of the ring affects the direction of the shielding cone.

The five-membered rings **67-71** followed the model and the expected ΔCF_3 values were observed even in the case of **69** or **71** which included more functional groups. The boc-protected ester **72** displayed a 0 ppm ΔCF_3 difference. Possibly the sterically demanding boc-group changes the conformation equilibrium which is in an agreement with low observed $\Delta\delta^{PM}$ in the ^1H NMR spectrum. The phenyl-substituted pyrrolidine **73** followed the model, although the phenyl ring could influence the conformations and therefore ^{19}F NMR spectrum as well. Pyroglutamic ester **74** displayed positive +0.2 ppm difference which is not in the agreement with the model. In this case, the presence of the hydrogen bond between NH and CF_3 group or other acceptors cannot be ruled out. This hydrogen bond could explain the high observed $\Delta\delta^{PM}$ (+0.95) in ^1H NMR spectra (see **Figure 19**; compound **74**). The boc-phenylglycinol ester **77** does not follow the proposed model, although the negative ΔCF_3 value is in an agreement with the different conformational model (vide infra).

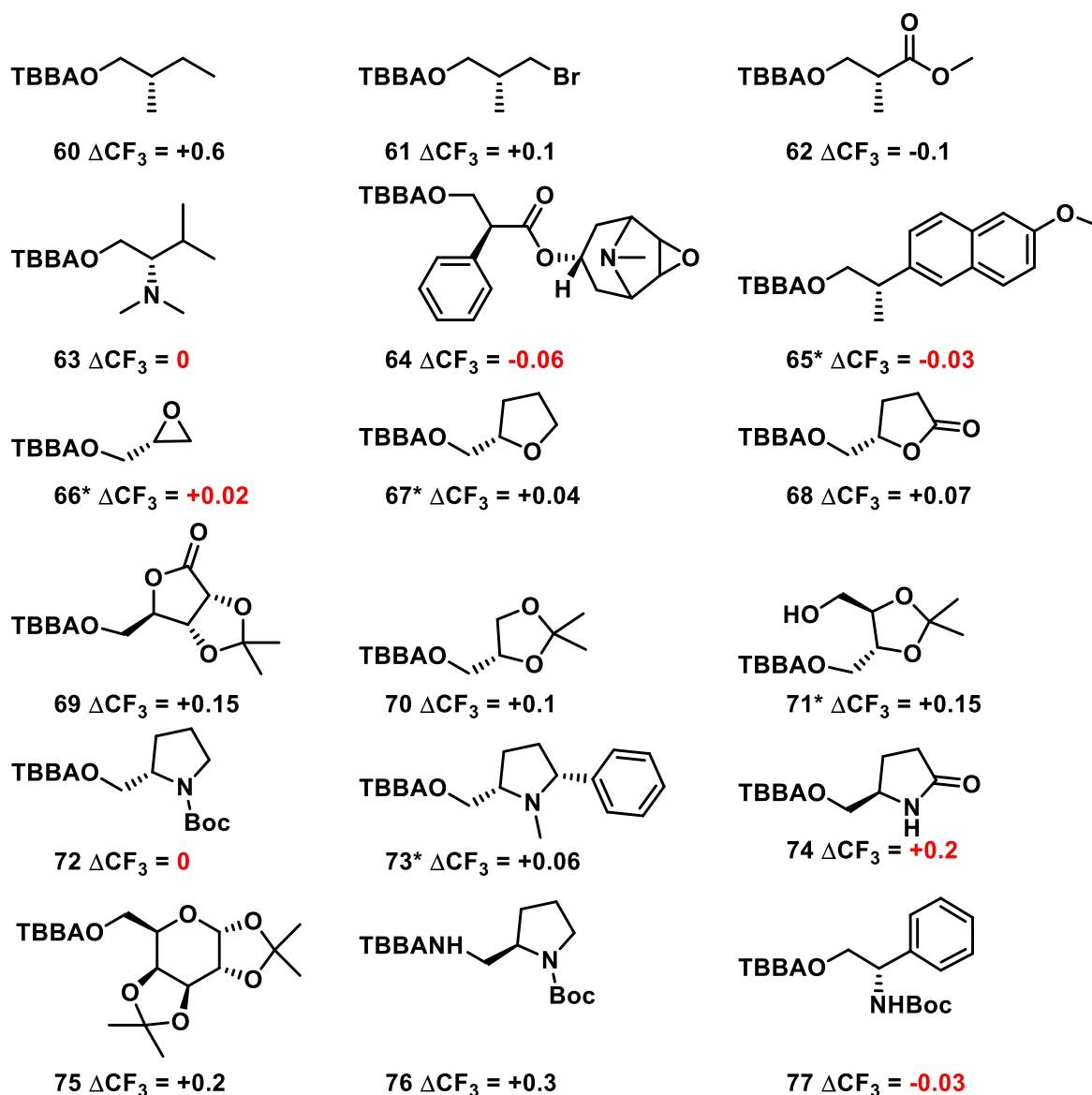


Figure 26 Observed ΔCF_3 for compounds **60-77**. Differences not matching the expected model are shown in red

The ^{19}F NMR spectra of the rest of the prepared derivatives (boc-protected amino alcohols and phenylglycinol derivatives) were analyzed as well (**Figure 27**). However, in those cases, almost a half (6 out of 14) of prepared derivatives display inconsistent chemical shift differences in the ^{19}F spectra and these differences cannot be easily translated to the absolute configuration of the chiral center as in the case of α -chiral derivatives.

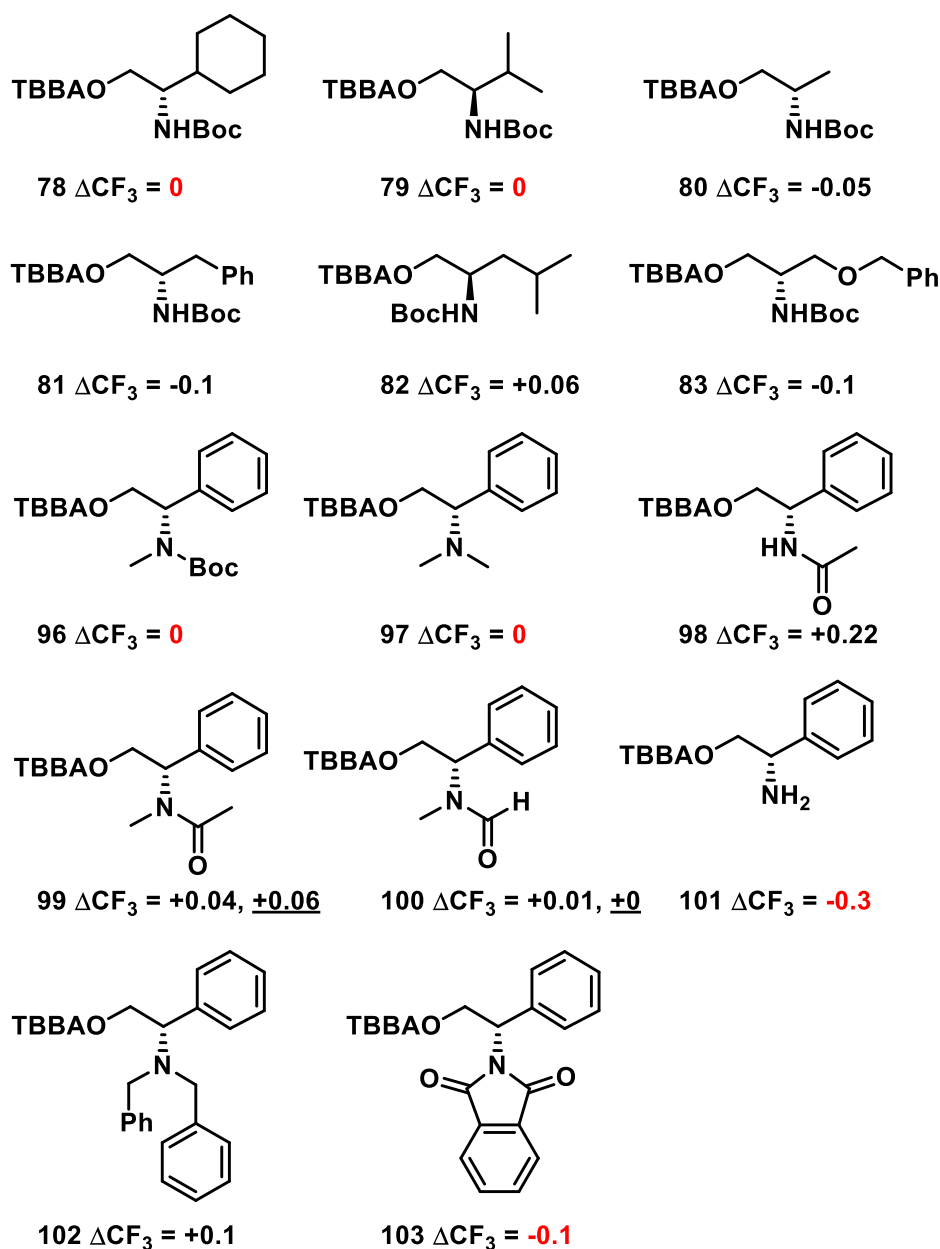


Figure 27 Observed ΔCF_3 of compounds **78-83** and **96-103** Differences not matching the expected model are shown in red

3.5.2.6. Computational investigation of the conformation of the *N*-boc amino alcohols

Last, the supposed effect of the boc group on the conformation equilibrium of compound **77** was studied in-silico. The theoretical lowest-energy conformers were identified using Spartan 18 (B3LYP-D3/6-31G*). The simulation revealed that the boc group is always located outside of the shielding zone in agreement with the observed chemical shifts of the boc group. The position of the phenyl group varies and depends on the presence of intramolecular hydrogen bonds. If hydrogen bonds are formed, then phenyl is positioned inside of the shielding zone (**Figure 28**) while in the case of no hydrogen bonds, the phenyl ring is located outside the shielding zone (**Figure 28b**).¹⁷⁹

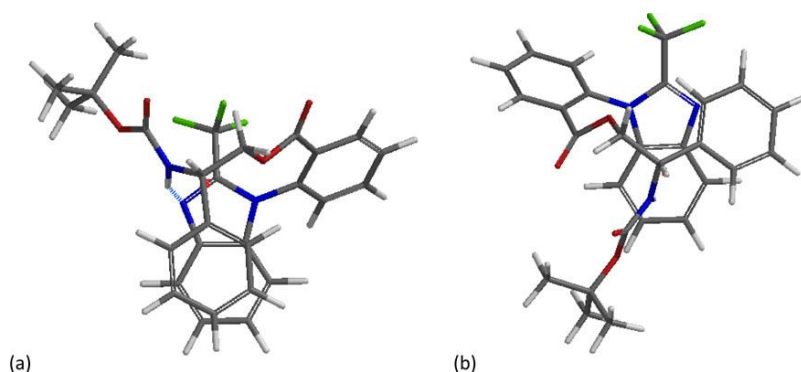


Figure 28: Theoretical lowest-energy conformers of **77** in a nonpolar solvent (software Spartan 18). The conformer distribution was calculated with the MMFF model (≤ 100 kJ/mol), followed by the calculation of energy at the ground state using DFT in a nonpolar solvent (B3LYP-D3/6-31G*) to account for long-range nonbonded dispersion interactions. Hydrogens were omitted for clarity. (a) Most stable conformer of (**P**)-**77** (Boltzmann weight: 0.901) with the hydrogen bond (light-blue dashed line) between the NHBoc and benzimidazole nitrogen. (b) Most stable conformer of (**M**)-**77** (Boltzmann weight: 0.627) without hydrogen bonds.

The calculation revealed the formation of intramolecular hydrogen bonds mainly between NHBoc and benzimidazole nitrogen at position 3. ^{19}F - ^1H NOESY NMR experiment was performed as well to rule out the possibility of the hydrogen bond between CF_3 and NH groups and no interaction was observed, therefore a significant interaction between those two groups can be excluded.¹⁷⁹

3.5.2.7. Investigation of the possible bonding interactions

To evaluate the presence of the hydrogen bond, we performed ^1H NMR experiments in different solvents and/or with additives. NMR experiments were conducted with compounds **77-83** and **96** as model substrates. At first, the NMR spectra were measured in acetone- D_6 which was considered as a competing hydrogen bond acceptor and therefore could cause the change in the conformation equilibrium by removing the possible conformation-stabilizing H-F interaction. Furthermore, methyl trifluoroacetate (TFAOMe) was added as a source of external trifluoromethyl group which could interact with the Boc carbonyl group of the substrates. Observed $\Delta\delta^{PM}$ values are depicted in **Figure 29**.

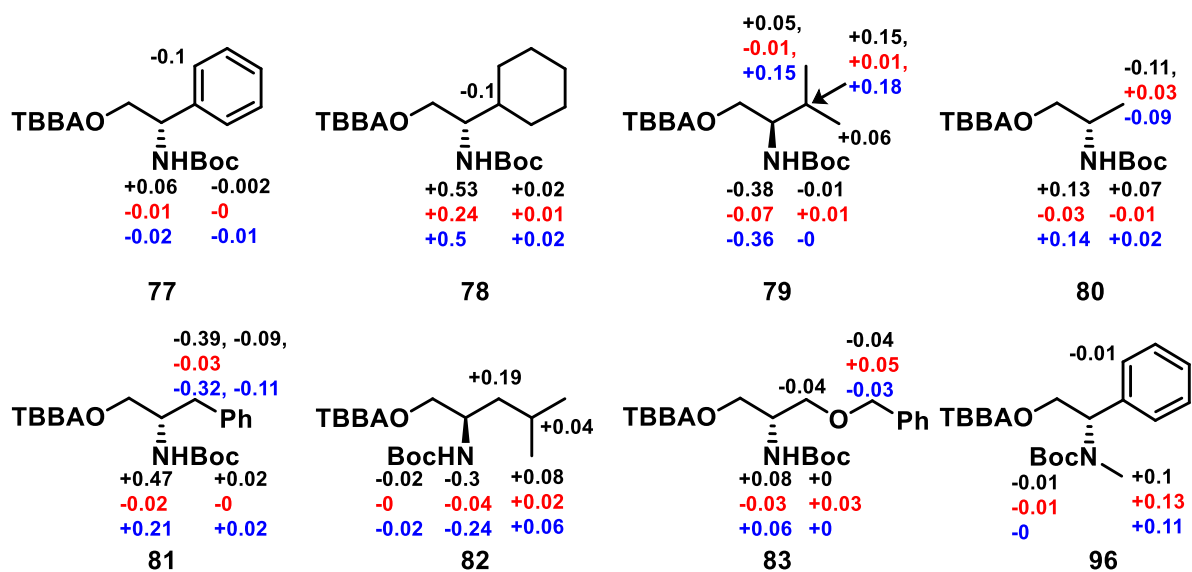


Figure 29 Observed $\Delta\delta^{PM}$ for compounds **77-83** and **96** in various solvents, black: CDCl_3 , red: acetone-D_6 , blue: $\text{CDCl}_3 + \text{TFAOMe}$

The observed $\Delta\delta^{PM}$ of **77** in acetone-D_6 displayed the correct signs, although the observed difference was small and close to the limits of the instrumentation. Similar situation was observed after the addition of TFAOMe into the CDCl_3 sample. Interestingly, in the case of derivative **78**, the sign of the $\Delta\delta^{PM}$ stayed the same as in the original spectra, although the magnitude of the difference was smaller. The $\Delta\delta^{PM}$ in the case of **79** became irregular in acetone-D_6 . At first, the $\Delta\delta^{PM}$ of the methyls in the isopropyl group become negative while the CH in the isopropyl group displayed positive +0.01 ppm difference. Similar irregularity was observed on the boc-amino group which displayed negative -0.07 ppm difference of the NH while the boc group displayed positive +0.01 ppm difference. The observed $\Delta\delta^{PM}$ after the addition of TFAOMe into the CDCl_3 sample displayed very similar values compared to the original CDCl_3 spectra without the additive.

Complete inversion of the $\Delta\delta^{PM}$ sign was observed in **80** when the spectrum was measured in acetone-D_6 although the difference was close to zero. The spectra of **80** with TFAOMe in CDCl_3 displayed almost identical $\Delta\delta^{PM}$ as the original sample. Similar effect was observed in the case of compound **81**. No inversion of $\Delta\delta^{PM}$ was observed in the case of compound **82**. The observed $\Delta\delta^{PM}$ in acetone-D_6 were significantly smaller compared to spectra in CDCl_3 (e.g., -0.04 vs -0.3 ppm for NH). The addition of TFAOMe did not have a significant effect. Partial inversion was observed in the case of compound **83**. The $\Delta\delta^{PM}$ at the benzylic position and NH were inverted in acetone-D_6 compared to CDCl_3 . Nevertheless, the boc-group displayed non-inverted positive $\Delta\delta^{PM}$ and no significant change was observed after the addition of TFAOMe. The low effect of the acetone on the $\Delta\delta^{PM}$ of compound **83** possibly originates from competitive formation of the hydrogen bond between the NH and ether oxygen.

Elimination of intramolecular hydrogen bond formation in the case of compound **96** led to marginal $\Delta\delta^{PM}$ differences between the NMR spectra in CDCl_3 and acetone- D_6 solutions.

Those results suggested the hydrogen bond might be present in the compounds although it is not likely the only cause of the obtained opposite configuration in the boc-protected amino alcohols. This can be seen in the examples in **Figure 29**. Conducting the NMR measurement in acetone- D_6 had a significant effect on the observed $\Delta\delta^{PM}$, although not all the derivatives displayed fully inverted $\Delta\delta^{PM}$. This suggests the presence of other interactions. TFAOMe (as an external CF_3 source) had only a marginal effect on the chemical shifts. Dibenzyl derivative **102** (**Figure 25**) followed the proposed model. It displayed an anomalous value at one of the benzylic protons while ^{13}C spectra showed the expected sign. Phthalimide **103** (**Figure 25**) displayed a mix of positive and negative $\Delta\delta^{PM}$ values which would make the assignment of absolute configuration impossible or at least very speculative. **103** does not contain acidic NH within its structure. The sterically less demanding derivatives **97** and **101** (**Figure 25**) fully followed the proposed model. The *N*-methyl derivatives **96**, **99**, and **100** displayed a mix of positive and negative $\Delta\delta^{PM}$ values due to the complex conformational equilibrium with various amide rotamers.

The observed change in $\Delta\delta^{PM}$ (**Figure 29**) supports the formation of hydrogen bonds, however the influence of the steric hinderance (**80** vs **81**, **Figure 29**) is also evident. The increased acidity of the hydrogen atom in the carbamate or amide functionality has a strong influence on the formation of hydrogen bonds capable of changing the conformational equilibrium. Moreover, the repulsion between the *N*-carbonyl moiety and trifluorobenzimidazole ring significantly impacts the conformer ratio. Both effects cause incorrect assignment since the resulting predominant conformers differ from the general conformational model.

Based on the experimental results and the *in-silico* modeling an alternative conformation model for *N*-Boc amino alcohols was proposed (**Figure 30**).

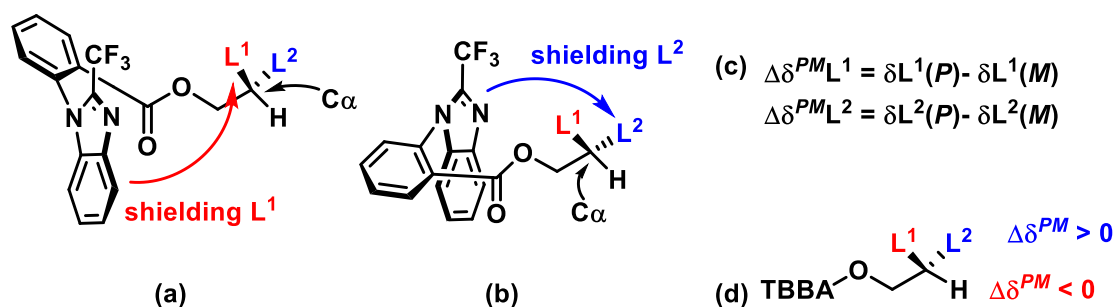


Figure 30 Conformational model for the analysis of the boc-substituted derivatives

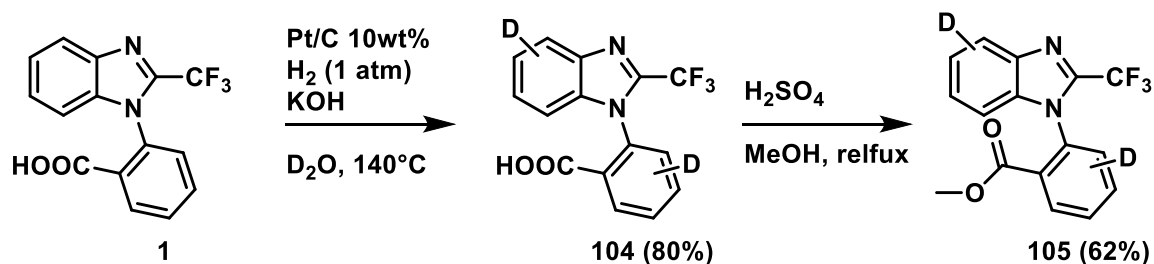
In this model, the proton at C_α and the ester carbonyl group are in *syn*-periplanar conformation which moves one of the substituents into the shielding zone of the benzimidazole (**Figure 30a/b**). Compared to the previously devised model for β -chiral esters, the rotation around $\text{C}_\alpha\text{-CH}_2\text{O}$ bond causes the

shielding effect to be projected towards the opposite substituents. The shielding/deshielding $\Delta\delta^{PM}$ is calculated in a same way as in the other models (**Figure 30c**) and the simplified model is shown in **Figure 30d**. Importantly, the model is suitable for compounds containing NHCOR (i.e. Amide, carbamate) as one of the substituents. The presence of the more acidic hydrogen causes likely the formation of hydrogen bonds which change the preferred conformer and the observed $\Delta\delta^{PM}$ values.

In case of *N*-disubstituted derivatives with R-NCOR', the conformation equilibrium is more complex due to the formation of amide bond rotamers and the observed $\Delta\delta^{PM}$ does not allow clear configuration assignment.

3.5.3. Synthesis of deuterated TBBA

Later, the deuterated version of TBBA **104** was prepared using high-pressure hydrogen deuterium exchange (Scheme 17).¹⁸⁰ Possibly the H \rightarrow D exchange could simplify the analysis of the ¹H NMR spectra of the TBBA derivatives.



Scheme 17 Synthesis of deuterated derivatives **104** and **105**

At first, TBBA **1** was dissolved in D₂O in the presence of 1eq. of KOH due to the low solubility of TBBA in water. Heating for 24 hours in an autoclave in the presence of Pt catalyst and hydrogen atmosphere yielded TBBA-D₆ **104**. The extent of deuteration was confirmed by HRMS and 6 deuterium atoms were exchanged (**Figure 31**). Furthermore, the deuterated compound **104** was converted into the methyl ester **105**. Integration of the ¹H NMR spectra suggested 25% deuterium incorporation at two positions, 90% incorporation at another two positions and full deuteration on the remaining four. This suggests presence of multiple derivatives with various extent of deuteration.

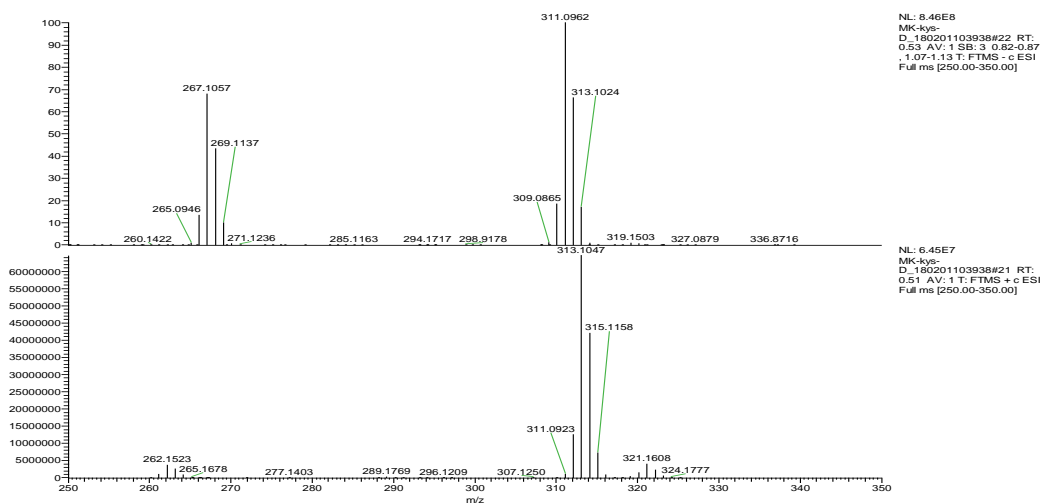


Figure 31 HRMS spectra of **104**, top: ESI(-), bottom: ESI(+)

Possibly increase of the reaction time could yield the fully deuterated derivative, however because the reaction could be performed only at low scale and the conditions were not compatible with the use of enantiopure TBBA, this approach was abandoned.

3.5.4. Conclusion

In conclusion, the novel CDA for absolute configuration assignment by NMR was developed. The conformational model was validated on a set of seventeen α -chiral esters and amides which allows the configuration assignment by means of ^1H , ^{13}C , and ^{19}F NMR spectroscopy.

A similar model was developed for β -chiral compounds and was validated on a set of eighteen compounds. Seventeen of them fully followed the model while in one case, an opposite configuration was obtained. Further investigation of fifteen derivatives revealed the different conformation preference for *N*-*boc* amino alcohols and *N*-acyl amino alcohols. This conformational preference is likely caused by the hydrogen bond between NH and CF_3 or benzimidazole nitrogen, as suggested by *in-silico* modelling, in combination with steric repulsion between the N-carbonyl and trifluoromethyl group and benzimidazole heterocyclic system. This hypothesis was supported by the ^1H NMR spectra measured in acetone- D_6 as an external hydrogen bond acceptor which caused significant changes in the observed $\Delta\delta^{PM}$ compared to CDCl_3 . However, no direct ^1H - ^{19}F interaction was observed in H-F NOESY NMR. Based on the experimental data and *in-silico* modelling, an alternative conformational model was proposed for the amino alcohols with the *N*-carbonyl moiety. Unfortunately, compounds of the R-N-COR or RCO-N-OCR type of functional groups did not follow any proposed models and provided highly anomalous $\Delta\delta^{PM}$.

The removal of the protecting group changed the conformation equilibrium again. The unprotected compound followed the general model for β -chiral compounds which allowed for two subsequent analyses one of the protected compounds using the modified model and another one using deprotected

amino alcohol ester and the unmodified model. Unfortunately, the ^{19}F NMR yields ambiguous results and, therefore, cannot be recommended for this type of compounds.

4. Results and discussion: Project catalysis

4.1. Design of the ligand

Two structures of the ligand (**Figure 32**) were envisioned at first. The benzimidazol-2-one/thione **106** which was reported multiple times as a ligand for Pd-catalyzed or organocatalytic reactions.^{60,181-183} The benzimidazole-pyridine ligand **107** is based on pyridine-oxazoline catalyst developed by Kočovský.¹²⁵

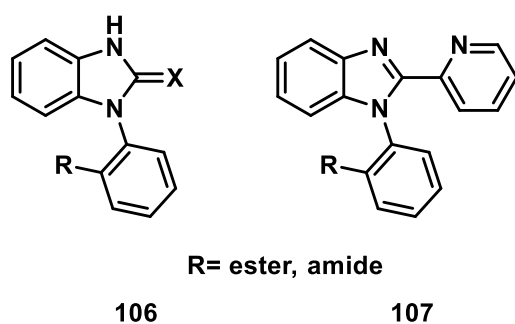
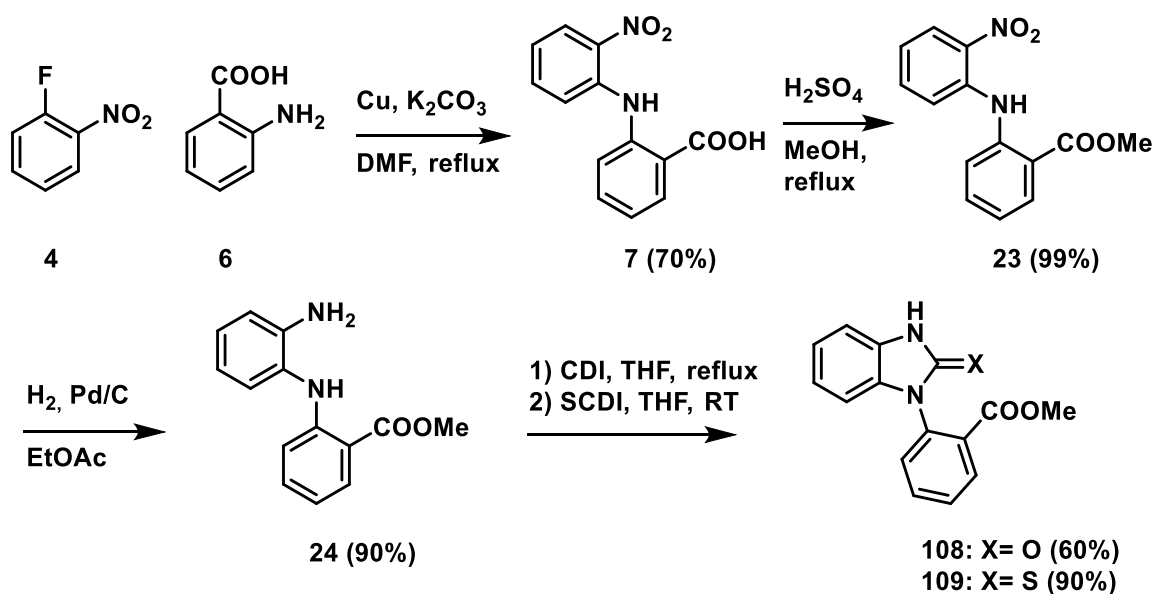


Figure 32 Proposed structures of the ligands

While the synthesis of the ligand **106**, could be conducted under copper-catalyzed Chan-Lam arylation,¹³¹ a different approach was chosen for the following reasons: a) the arylation yielded a significant amount of diarylated product,¹³¹ b) the subsequent oxidation of the methyl group to the carboxyl was expected to be problematic based on the previous attempts, and c) the requirement to use column chromatography could be problematic for obtaining enough material to develop a chiral resolution method. For those reasons, the cyclization-based synthesis was developed (**Scheme 18**).

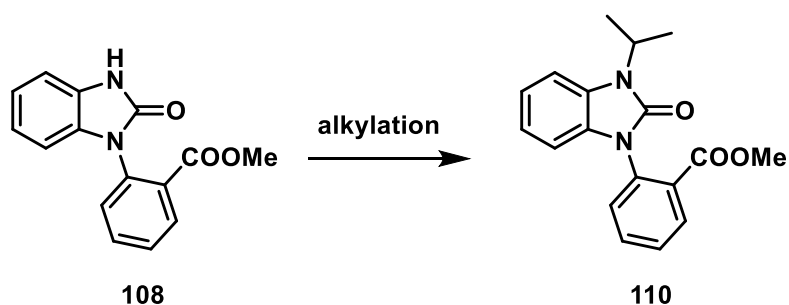


Scheme 18 Synthesis of **108** and **109**

4.2. Synthesis of benzimidazolone based ligand

The synthesis started with the copper catalyzed arylation of anthranilic acid **6** to yield nitro acid **7**, which was converted to methyl ester **23** using common acid catalyzed esterification. The esterification was followed by the catalytic hydrogenation in ethyl acetate to yield diamino ester **24**. The final product **108** was formed by the cyclization with carbonyldiimidazole (CDI) in refluxing THF and sulfur analog **109** with thiocarbonyldiimidazole in THF at room temperature. The purification of **108** required column chromatography since multiple byproducts were observed. For this reason, further optimization was performed to see if better conditions could be devised.

Later it was decided to further modify the structure by the alkylation on the benzimidazole nitrogen. Based on the previous results,¹⁸⁴ the direct alkylation was expected to yield a mixture of products; nevertheless, two attempts were made to see if direct alkylation was possible or not to yield **110**.



Scheme 19 Proposed synthesis of **110**

At first, the Mitsunobu conditions were used (DIAD, PPh₃, THF). The starting material was not fully consumed overnight while two products were detected in HPLC-MS analysis in the approximately same amount. Further addition of more PPh₃, DIAD and alcohol did not improve the conversion. The products were not isolated since their separation by column chromatography was not possible. The structure of *N*- and *O*-isopropyl regioisomers was suggested based on the LCMS analysis (**Figure 33**). Similar results were obtained with isopropyl iodide and sodium hydride as a base in THF.

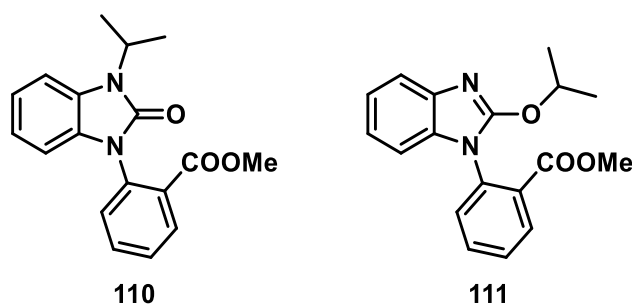
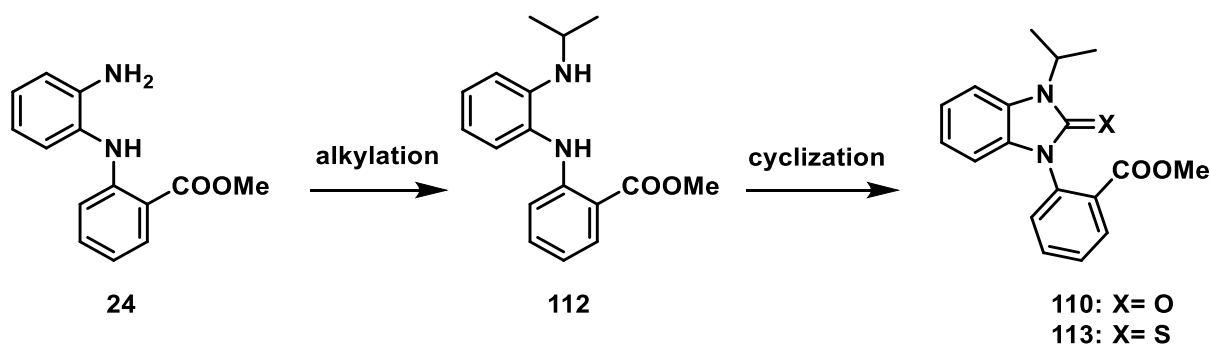


Figure 33 Proposed structure of the products of alkylation of **108**

In this approach, the isopropyl group was introduced earlier in the sequence followed by the cyclization with suitable reagent. The approach is depicted in **Scheme 20**. The synthesis started as before but reduced intermediate **24** was alkylated using various conditions.



Scheme 20 Proposed synthesis of **110** and **113**

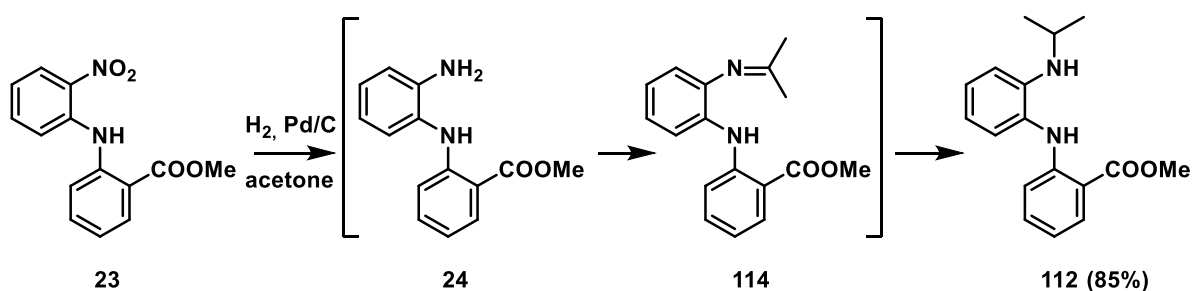
Table 17 Initial attempts to synthesize **112**

Entry	Conditions	Result
1 ¹⁸⁵	Acetone, DCE, NaBH(OAc) ₃ , HOAc	15% conversion ^a
2	Acetone, THF, NaBH ₄	No reaction

^a by HPLC

The results of the direct alkylation are summarized in **Table 17**. The reductive amination with NaBH(OAc)₃ in the presence of the acetic acid in dichloroethane showed low conversion (entry 1) while the use of NaBH₄ as a reducing agent did not yield any product at all (entry 2). Possibly, the residual water in acetone was the cause for low conversion and therefore other reducing agents were investigated.

Due to good experience with catalytic hydrogenation of nitro group, it was assumed the possibility of reductive alkylation via *in situ* formed imine **114**. This idea was expanded to development of one pot protocol of direct conversion of nitro ester **23** to isopropyl derivative **112** (Scheme 21).



Scheme 21 One pot reduction/reductive amination

This protocol consisted of *in situ* preparation of amino ester **24** from nitro ester **23** followed by imine **114** formation which would be reduced by catalytic hydrogenation to yield amine **112**. The optimization procedures are summarized in **Table 18**.

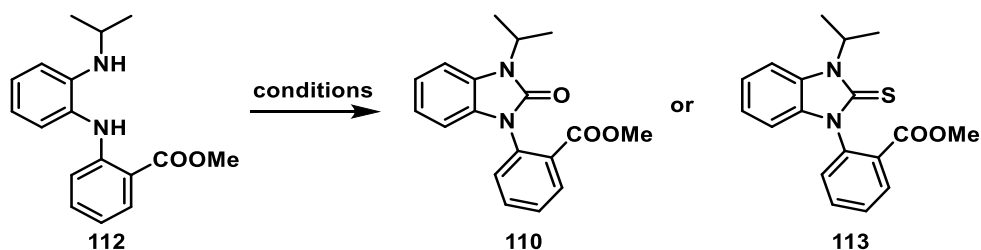
Table 18 Optimization of the reductive amination from **23** to amine **112**

Entry	Eq. Pd/C	Concentration	Additive	Results
1	5%	0.025M	--	^a 50% conversion of 23 , not isolated
2	5%	0.05M	HOAc cat. (3 “drops”)	60% isolated yield
3	5%	0.05M	HOAc 1.5 eq.	97% isolated yield
4	2.5%	0.05M	HOAc 1.5 eq	94% isolated yield
5	2.5%	0.075M	HOAc 1.5 eq	95% isolated yield

^a by HPLC

At first, the reduction was conducted in acetone instead of ethyl acetate and partial conversion was observed in HPLC-MS after 24 hours (entry 1). No byproducts were observed suggesting the low conversion was due to slow formation of imine **114**. Addition of the catalytic amount of acetic acid and increase in the reaction concentration improved the reaction rate and the starting material was fully converted into the product. The product was fully isolated in 60% yield after column chromatography. Because the reaction was conducted on a small scale (20 mg), the exact amount of acetic acid in the reaction was not known. Therefore, the reaction was conducted on a larger scale and a more exact amount of acid was added. The use of 1.5 equivalent of acid (entry 3) further increased the conversion of the starting material into the product. Furthermore, full conversion was observed, and the product was isolated by simple filtration through pad of celite and evaporation of the solvent. Residual acetic acid remained in the evaporation residue. For this reason, the oily residue was dissolved in ethyl acetate and extracted with carbonate solution and evaporated again to yield the product in the high yield (entry 3).

Further, the amount of the catalyst was reduced to 2.5 mol% (entry 4), which did not have any effect on the isolated yield. The concentration of the reaction mixture was further increased to 0.075M and again, no effect on the isolated yield was observed (entry 5). This reaction was scaled up to the 9 g scale. The cyclization of the isopropyl ester **112** to benzimidazole derivatives **110** and **113** were then performed (**Scheme 22**).



Scheme 22 Synthesis of benzimidazole derivatives **110** and **113**

The previously used conditions were not suitable for the synthesis of **110** or **113** and therefore new set of optimizations was performed. The performed reactions leading to **110** are summarized in **Table 19**.

Table 19 Cyclization to **110**

Entry	Conditions	Results
1	CDI, THF, reflux	^a 10 % conversion
2	Ethyl chloroformate, TEA, DCM	No reaction
3	Triphosgene, DCM, RT	^a 40% conversion
4	Triphosgene, pyridine, DCM, RT	85% isolated yield
5	Triphosgene, DIEA, DCM, RT	85% isolated yield
6	Triphosgene, TEA, DCM, RT	85% isolated yield
7	Phosgene (15% in toluene), TEA, DCM	90% isolated yield
8	Triphosgene, TEA, DCM, RT, scale-up	95% isolated yield

^a by HPLC

The previously used cyclization using CDI in refluxing THF provided only low conversion of the starting material (entry 1). The reaction between starting material **103** and ethyl chloroformate in DCM at room temperature did not yield any product at all (entry 2), not even the ethyl carbamate intermediate was detected. Possibly residual moisture was the cause of no observed reaction.

For this reason, more reactive triphosgene was used. The reaction without any external base resulted in 40% HPLC conversion (entry 3). Likely, HCl formed in situ from the reaction was protonating the amine which made it unreactive. The addition of an external base proved beneficial (entries 4-6). Three bases were investigated: pyridine (entry 4), diisopropylethylamine (entry 5), and triethylamine (entry 6). No measurable difference between those bases was observed. Triethylamine was used for the scale-up reaction: pyridine being UV active complicates the TLC/HPLC analysis and the price of DIEA was higher compared to TEA. Furthermore, a phosgene solution in toluene was used which was assumed to

be more reactive compared to triphosgene (entry 7). The product was isolated in 80% yield, which was comparable to isolated yields using triphosgene (entries 4-6). Although the yield using phosgene was slightly higher (90%) compared to triphosgene. In the end, triphosgene was used for the scale-up reaction due to safety concerns and ease of handling. The product of the scale-up reaction (entry 8) was isolated in 95% yield.

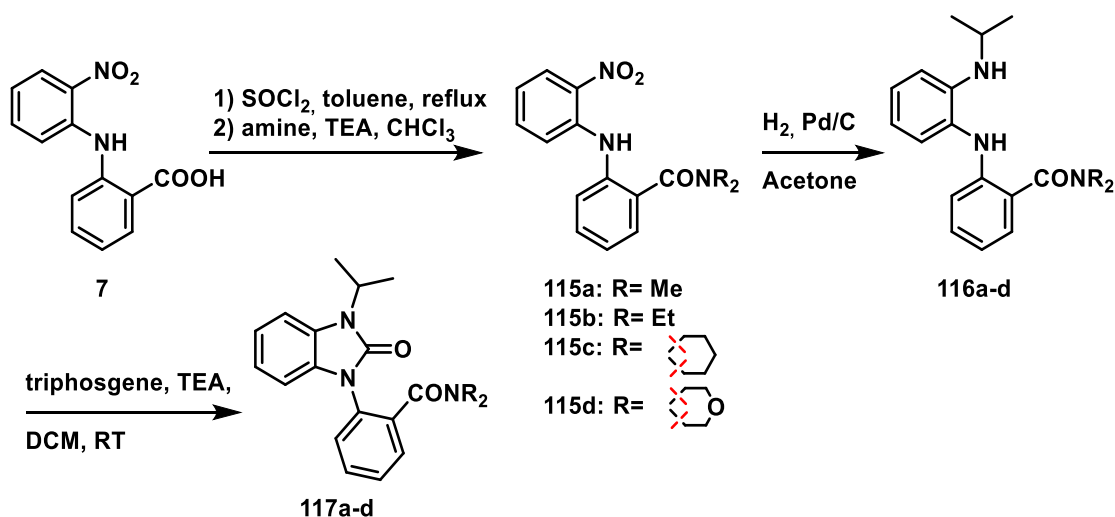
The cyclization leading to **113** was also more complex. The results are summarized in **Table 20**. The reaction with thiocarbonyldiimidazole in THF at the room temperature did show any conversion of the starting material (entry 1). Increasing the reaction temperature to reflux did not offer any improvements (entry 2). Further addition of the base (entry 3) did not show any conversion as well. For this reason, more reactive, although toxic, thiophosgene was used. At first, traces of product were observed when using triethylamine as a base at room temperature (entry 4). Increasing the temperature to reflux provided slight improvement and the product was isolated in 35% yield after column chromatography. Interestingly, using inorganic base¹⁸¹ further improved the reaction yield to 50% after column chromatography. The reaction was later scaled-up to a 2.4-gram scale and improved purification by crystallization from EtOH was developed which improved the yield to 75%.

Table 20 Cyclization to **113**

Entry	Conditions	Result
1	SCDI, THF, RT	No reaction
2	SCDI, THF, reflux	No reaction
3	SCDI, TEA, THF, reflux	No reaction
4	Thiophosgene, TEA, THF, RT	Traces ^a
5	Thiophosgene, TEA, THF reflux	35% ^a
6 ¹⁸¹	Thiophosgene, NaHCO ₃ , THF	50% ^a
7 ¹⁸¹	Thiophosgene, NaHCO ₃ , THF, scale-up	75% ^a

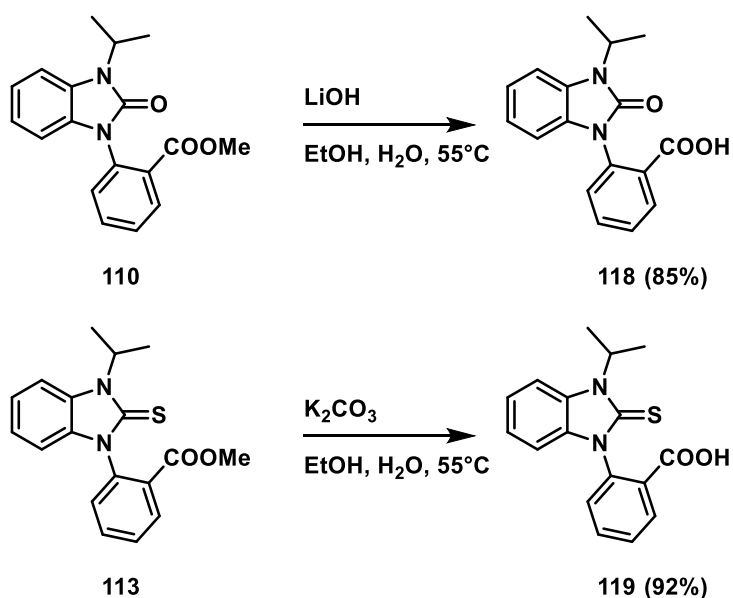
^a by HPLC

Several other derivatives were prepared using similar methodology (**Scheme 23**). The nitro acid **7** was converted into acyl chloride using SOCl₂ in toluene at reflux. This acyl chloride was treated with various amines in the presence of triethylamine in CHCl₃. This acylation yielded amides **115a-d** in high yields (from 90% to quantitative). The nitro amides **115a-d** were alkylated using the previously described reductive alkylation with acetone, acetic acid, and palladium on carbon using hydrogen gas as a reducing agent. The alkylated amides **116a-d** were isolated in 50-60% yield after column chromatography. The reaction was slower with the amide compared to the ester alkylation and therefore unreacted starting material had to be removed via chromatography. The cyclization with triphosgene in DCM was performed as previously described for the methyl ester **110** and the products **117a-d** were isolated in high yields.



Scheme 23 Synthesis of amide derivatives

This approach was later found unsuitable. Firstly, the prepared amides would not be possible to separate into enantiomers apart from chiral HPLC which is not suitable for larger amounts of the compound and second, the synthesis of each derivative required multiple steps. It was modified into a more diversity-oriented approach which would allow to prepare the various derivatives in a single step. The alternative synthesis was devised: the methyl ester was hydrolyzed to yield free acid **118** or **119** (**Scheme 24**) which could be separated into enantiomers by crystallization and further diversified using common esterification or amidation methods.



Scheme 24 Synthesis of carboxylic acids **118** and **119**

Ester **110** was hydrolyzed using LiOH in EtOH / H₂O mixture at 55 °C and after the neutralization the acid was isolated in 85% yield. Multiple approaches were tested for hydrolysis of the ester **113**. The hydrolysis is summarized in Table 21.

Table 21 Hydrolysis of **110**

Entry	Conditions	Results
1	LiOH, EtOH, H ₂ O, 55°C	55% isolated yield
2 ¹⁸⁶	TMSOK, THF, RT	95% isolated yield (as K ⁺ salt)
3	K ₂ CO ₃ , EtOH, H ₂ O, reflux	87% isolated yield
4	K ₂ CO ₃ , EtOH, H ₂ O, reflux, scale-up	92% isolated yield

At first, the same conditions were used as for the hydrolysis of **110** (entry 1). After the acidification and extraction, the product was isolated in 55% yield. TMSOK in THF¹⁸⁶ was used alternatively and the product was isolated as a potassium salt of the acid as was clear from a different NMR spectra of the product (**Figure 34**). The yield of the salt was 95% (entry 2). The hydrolysis was further conducted using K₂CO₃ in EtOH / H₂O mixture at reflux (entry 3). The product was isolated in 87% yield and in 92% after scaling up to 1.5 g scale (entry 4).

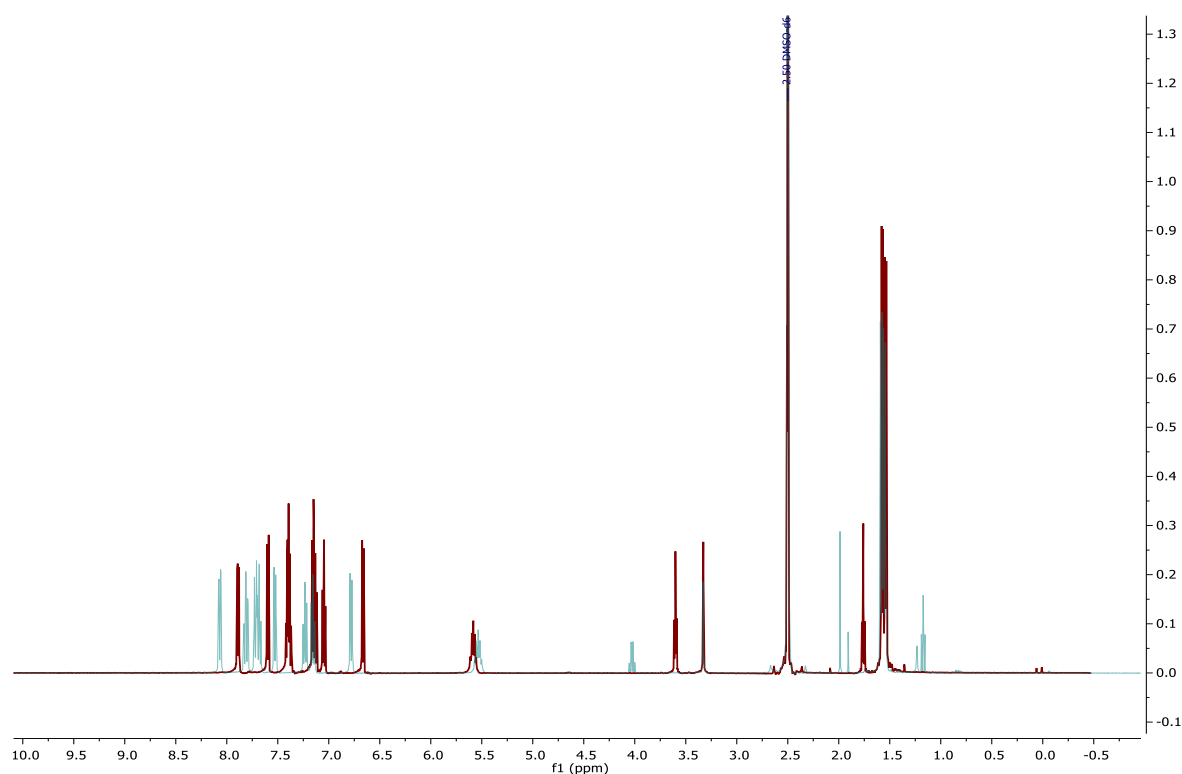


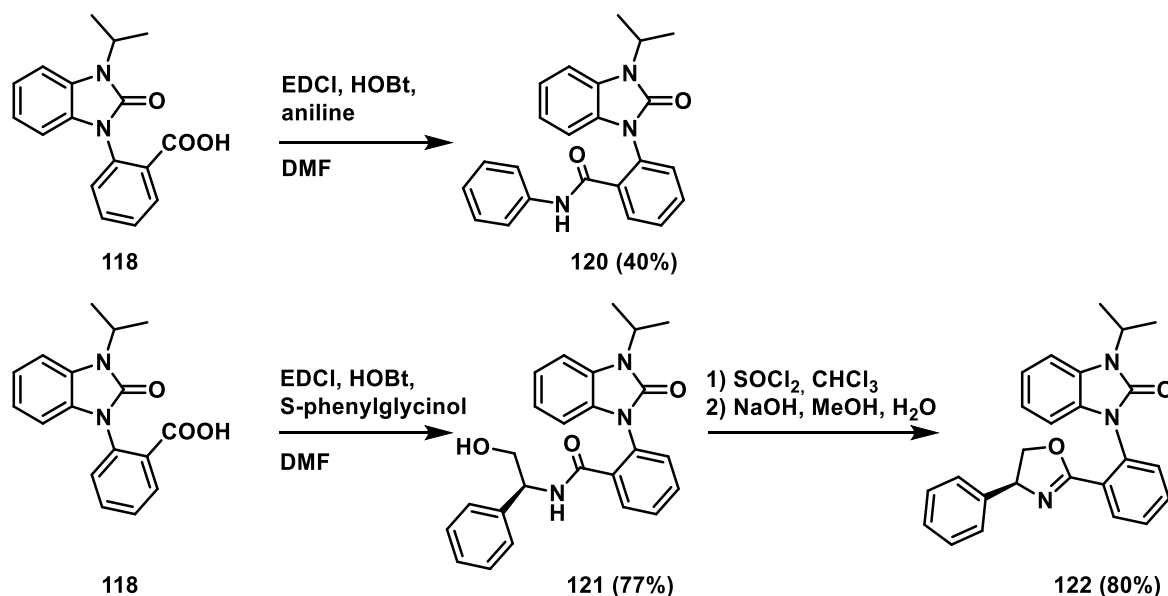
Figure 34 Red: Potassium salt of **119**, blue: acid **119**

The acid **118** was further modified by an acylation reaction (**Scheme 25**). Multiple conditions were tested (**Table 22**). Simple aniline acylation was used as a model reaction. DCC, DMAP yielded product **120** in 40% yield after column chromatography (entry 1). T3P in EtOAc and in DMF (entries 2 and 3) yielded the product **120** in 53 and 51% yield after extractive workup. The acid activation using carbonyldiimidazole (entry 4) and thiocarbonyldiimidazole (entry 5) did not yield any product at all. The use of more reactive HATU activator yielded product in 56% yield (entry 6) Last, the use of EDCI/HOBt in DMF provided the anilide **120** in 60% yield after the column chromatography (entry 7).

Table 22

Entry	Conditions	Results
1	DCC, DMAP, DCM	42% isolated yield
2	T3P, EtOAc, Pyridine	53% isolated yield
3	T3P, DMF, Pyridine	51% isolated yield
4	CDI, THF	No reaction
5	SCDI, THF	No reaction
6	HATU, DIEA, DMF	56% isolated yield
7	EDCI, HOBt, DMF	60% isolated yield

The acid **118** was also converted into the (*S*)-phenylglycinol amide **121** in 77% yield after extractive workup (**Scheme 25**). No separation of diastereomers was observed by HPLC or TLC. The NMR of the product **121** displayed a mixture of diastereomers in the 10:3 ratio suggesting a kinetic resolution and/or interconversion of the enantiomers (**Figure 35**). Unfortunately, no HPLC or TLC separation was observed for the oxazoline **122** which made this approach unsuitable for the preparative separation of the enantiomers.



Scheme 25 Derivatization of **118**

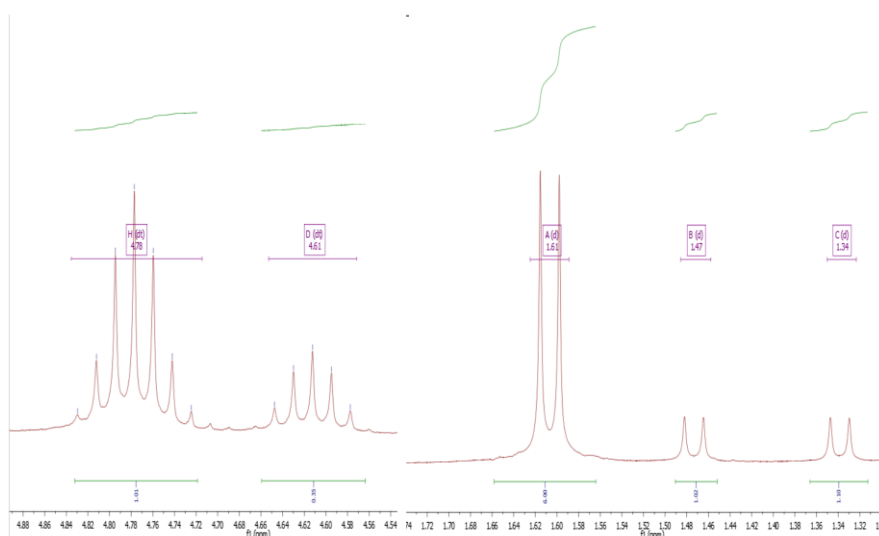
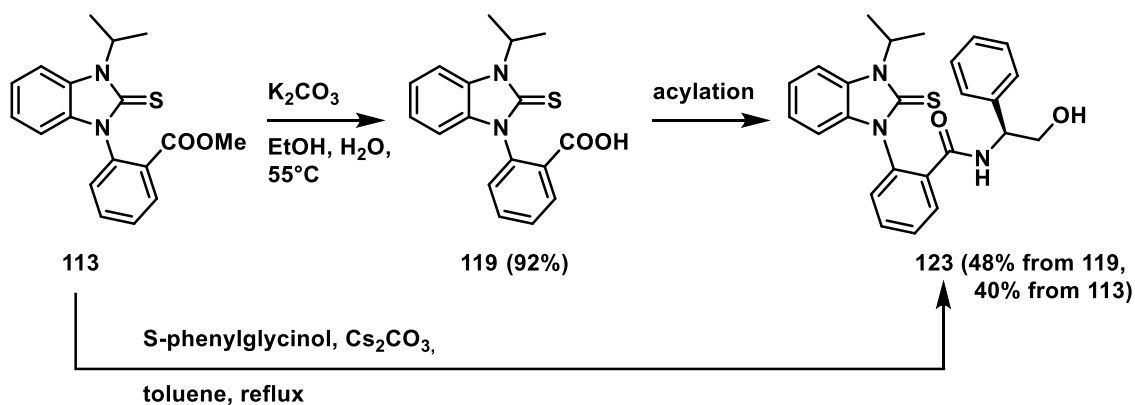


Figure 35 Detail of the $^1\text{H-NMR}$ spectra of **121**

Analogous procedure was designed towards the thio derivative **123**. Two approaches were attempted (**Scheme 26**). The two-step protocol including previously described hydrolysis of the methyl ester **113** followed by acylation of (*S*)-phenylglycinol or direct one step amidation of the methyl ester. While the hydrolysis of ester **113** to acid **119** was already developed, the direct amidation could save time and possibly increase the final yield of amide **123**.



Scheme 26 Synthesis of **123**

Multiple conditions were tried for the direct amidation of ester **113** (**Table 23**). At first, heating of the ester in the presence of potassium phosphate and (*S*)-phenylglycinol in isopropyl alcohol (entry 1) resulted in the hydrolysis of the ester to acid **119**. Traces of amide **123** were observed by TLC and HPLC. The use of Cesium carbonate in toluene improved the reaction and the amide was isolated in 70% yield. Importantly, the separation of the diastereomers was possible using column chromatography.

The scale-up of the reaction from 0.5 mmol to 2 mmol (entry 3) did not yield any product at all and full hydrolysis to acid **119** was observed. The cause was thought to be the presence of water or hydroxide in old Cs₂CO₃. The use of fresh Cs₂CO₃ from a new bottle proved beneficial and the reaction worked as expected (entry 4). Nevertheless, because the amidation was sensitive, the two-step procedure was adopted instead.

Table 23 Direct amidation of ester **113** to amide **123**

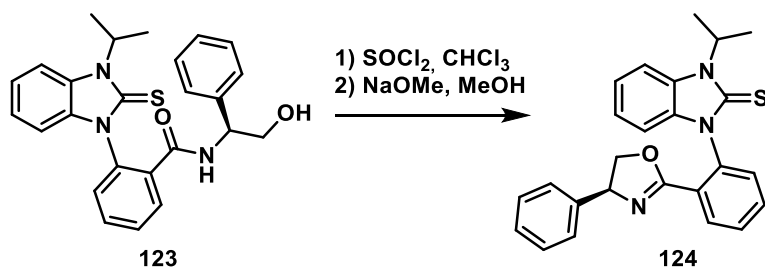
Entry	Conditions	Result
1	K ₂ PO ₄ , (<i>S</i>)-phenylglycinol, isopropyl alcohol, reflux	Hydrolysis to acid
2	Cs ₂ CO ₃ , (<i>S</i>)-phenylglycinol, toluene, reflux	70% isolated 123
3	Cs ₂ CO ₃ , (<i>S</i>)-phenylglycinol, toluene, reflux, scale-up	Hydrolysis to acid
4	“Fresh” Cs ₂ CO ₃ , <i>S</i> -phenylglycinol, toluene, reflux,	50% isolated 123

The acylation was performed under multiple conditions. The acylation was conducted using T3P or EDCI as activating agents. The use of T3P yielded a mixture of products (**Table 24**, entry 1) as did acylation with EDCI in DMF without any additive (entry 2). Addition of HOBt (entry 3) or DMAP (entry 4) was advantageous, and the product was isolated in high yield.

Table 24 Acylation of **119**

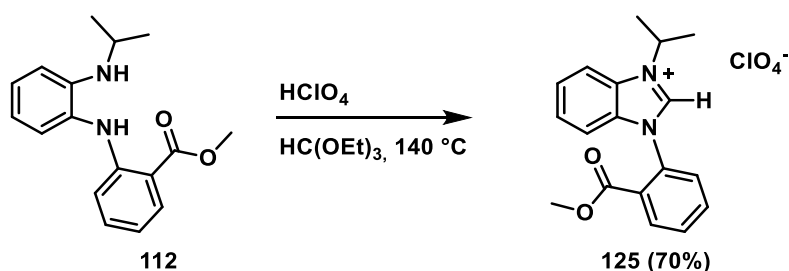
Entry	Conditions	Result
1	T3P, Pyridine, EtOAc, RT	Mixture of products
2	EDCI, DMF, RT	Mixture of products
3	EDCI, HOBt, DMF, RT	95%
4	EDCI, DMAP, DMF, RT	70%

Phenylglycinol amide **123** was then converted into oxazoline **124**, (**Scheme 27**) assuming better separation of the diastereomers. Unfortunately, the oxazolines **124** provided worse separation compared to **123**.



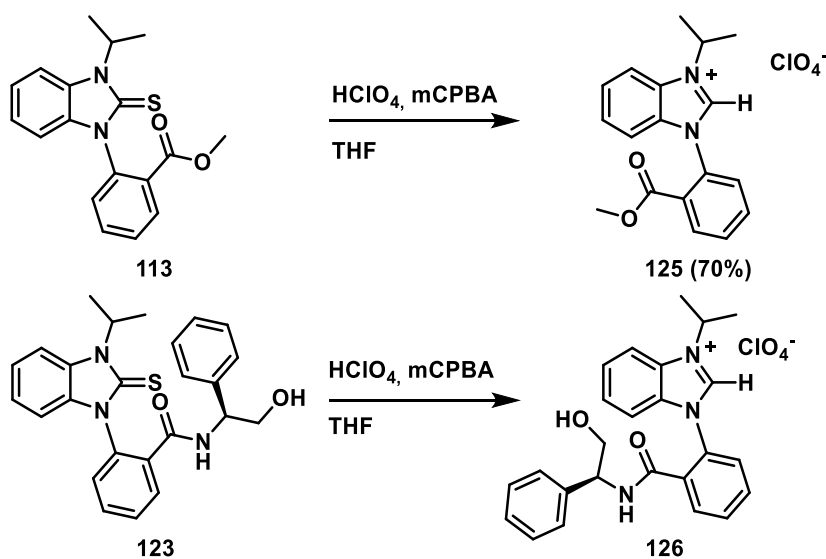
Scheme 27 Synthesis of **124**

Last, *N*-heterocyclic carbene precursors **125** and **126** were prepared. At first the precursor **125** was prepared by cyclization of **112** (scheme 28). The cyclization was conducted using triethyl orthoformate as a solvent and HClO₄ as a catalyst. The product was isolated in 70% yield.¹⁸⁷



Scheme 28 Synthesis of **125**

An alternative approach was the oxidation of derivatives **113** or **123** with *m*CPBA and HClO₄ in THF⁶⁰ (Scheme 29) to yield NHC precursor **125**. Compound **123** decomposed during oxidation. Unfortunately, the literature revealed racemization⁶⁰ of the prepared NHC even under mild conditions; therefore, this approach was abandoned.



Scheme 29 Synthesis of the NHC precursors

4.3. Synthesis of pyridine-based ligand

Because the preliminary results (*vide infra*) did not show any catalytic activity of the compound **111** and **113**, an alternative structure **127** was developed. Two possible synthetic disconnections were envisioned (Figure 36). The first possible pathway was metal catalyzed arylation reaction between 2-

pyridylbenzimidazole and suitable aryl halide (disconnection **127a**). The second option was cyclization of diamine such as **24** with suitable pyridine derivative (disconnection **127b**). The racemate **127** would be then resolved by a suitable method. This resolved core structure would then be modified to yield a library of various ligands.

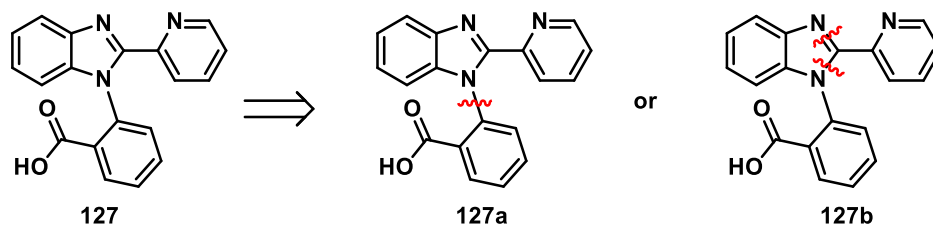
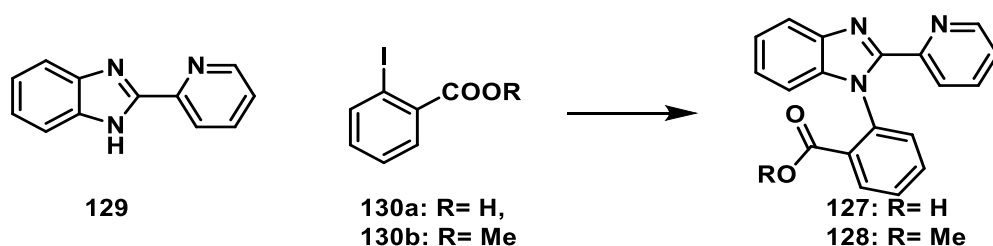


Figure 36 Disconnections leading to compound **127**

4.3.1. *N*-arylation based synthesis

At first, the arylation between 2-pyridylbenzimidazole **129** and iodobenzoic acid or its ester **130a/b** (Scheme 30) was attempted. Several reaction conditions were tested. (Table 25).



Scheme 30 Arylation of **129**

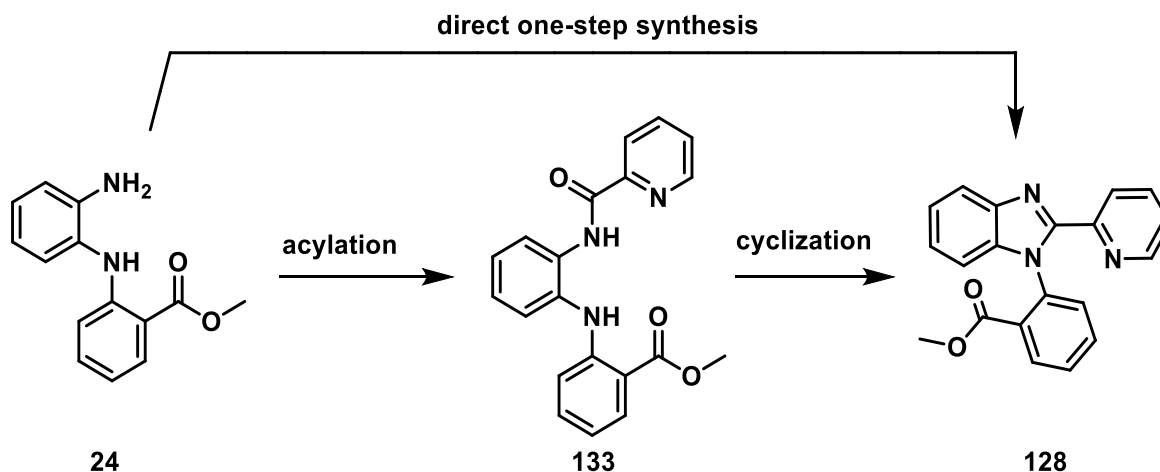
At first, the copper catalyzed arylation with L-proline as a catalyst was performed. The reaction was conducted in DMSO at 80°C (entry 1). Unfortunately, no product was observed under those conditions using iodobenzoic acid as an aryl halide partner. The presence of the free carboxylic acid group was thought to be problematic for the reaction; therefore, it was protected as a methyl ester. Nevertheless, under the same conditions using methyl ester **130b** (entry 2), no product was observed in HPLC analysis of the reaction mixture. Different reaction conditions (CuI, 1,10-phen, Cs₂CO₃, DMF, reflux) were tried as well (entries 3-4); however, even under those more forcing conditions, no product was observed.

Table 25 Arylation of **129**

Entry	Conditions	Result
1	CuI, L-proline, K ₂ CO ₃ , DMSO, 80°C, 130a ¹⁸⁸	No reaction
2	CuI, L-proline, K ₂ CO ₃ , DMSO, 80°C, 130b	No reaction
3	CuI, 1,10-phenanthroline, Cs ₂ CO ₃ , DMF, argon, reflux, 130a ¹⁸⁹	No reaction
4	CuI, 1,10-phenanthroline, Cs ₂ CO ₃ , DMF, argon, reflux, 130b ¹⁸⁹	No reaction

4.3.2. Cyclization approach

Alternatively, the cyclization of diamine **24** was developed at the same time (Scheme 31) and since it yielded better results, the arylation based synthesis was abandoned. Diamine **24** was prepared as previously described and subjected to various cyclization conditions (Table 26).



Scheme 31 Synthesis of **128**

Table 26 One step cyclization

Entry	Conditions	Result
1	PyCOOH, HOAc, reflux	Traces
2	PyCHO, H ₂ O ₂ , ACN, HCl ¹⁹⁰	Traces
3	PyCHO, H ₂ O ₂ , ACN, pTSA	No reaction
4	PyCHO, H ₂ O ₂ , ACN, TFA	No reaction
5	PyCHO, Na ₂ S ₂ O ₅ , DMA, 100°C ¹⁹¹	Traces
6	PyCHO, DMSO, 100°C ¹⁹²	No reaction
7	PyCHO, HOAc, reflux	Traces
8	PyCHO, Oxone, DMF, H ₂ O	50% isolated
9	PyCHO, EtOH, then I ₂ , K ₂ CO ₃ , DCM	80% isolated
10	PyCHO, EtOH, then I ₂ , K ₂ CO ₃ , DCM, scale-up	30% isolated

The cyclization in refluxing acetic acid yielded traces of the product (entry 1) while the rest of the mixture consisted of two byproducts. The suggested structures of byproducts **131** and **132** are depicted in Figure 37. Structure **131** was assumed based on mass from the MS spectra. The structure **132** was suggested as a reasonable product of cyclization of compound **131**. The compound did not ionize well in the MS; therefore, its m/z was not detected, therefore the structure is a suggestion based on the known reactivity.

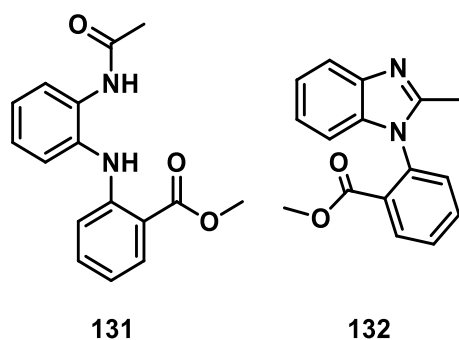


Figure 37 Proposed structures of byproducts **131** and **132**

The cyclization using pyridine-carbaldehyde with aq. HCl as a catalyst and H₂O₂ as an oxidant¹⁹⁰ (entry 2) yielded traces of the product together with a mixture of the starting material and hydrolyzed methyl ester derivatives. Because of the observed hydrolysis of the methyl ester, the aq. HCl was substituted for pTSA (entry 3). In this case, no reaction at all was observed. This was in accordance with the proposed reaction mechanism which involves formation of HOCl *in situ* as an active oxidant. The same was observed in the case of TFA being used as an acid catalyst for the reaction (entry 4).

The reaction of pyridine-2-carbaldehyde with Na₂S₂O₅ as a catalyst in dimethylacetamide at high temperature only yielded traces of the product (entry 5). The cyclization of the diamine **24** with pyridine-2-carbaldehyde in DMSO at elevated temperature, which was used in one of research groups in our department with success,¹⁹² did not yield any product at all (entry 6). The cyclization of pyridine-2-carbaldehyde in refluxing acetic acid with access of air as an oxidant showed traces of the product in HPLC analysis (entry 7).

Finally, the Oxone mediated cyclization¹⁹³ (entry 8) yielded the product in 50% yield. Furthermore, the two-stage procedure (entry 9) consisting of *in situ* formation of the imine followed by the iodine-mediated cyclization yielded the product **128** in slightly higher 80% yield. Unfortunately, the scale-up of the reaction did not proceed well and the product was isolated only in 30% yield (entry 10).

While it was possible to prepare the product **128** via direct cyclization, the problems with scale up and reproducibility forced us to explore another procedure. The two-step procedure was envisioned which included the acylation of **24** with pyridine-2-carboxylic acid followed by dehydrative cyclization of intermediate **133** towards final product **128** (Scheme 31).

The acylation was attempted under common conditions. At first, EDCI+DMAP were tried (**Table 27**, entry 1). Incomplete conversion of the starting material was observed. The use of T3P in EtOAc/pyridine yielded full conversion of the starting material into the product (entry 2) and product **133** was isolated in 80% yield. The reaction was further scaled up to 58 mmol scale (20 grams) and the product was isolated in high yield after simple acid/base extraction (entries 2-6).

Table 27 Acylation of **24**

Entry	Conditions	Result
1	EDCI, DMAP, DMF	incomplete conversion by HPLC
2	T3P, Pyridine, EtOAc, 1 mmol scale	80% isolated
3	T3P, Pyridine, EtOAc, 4 mmol scale	66% isolated
4	T3P, Pyridine, EtOAc, 12 mmol scale	77% isolated
5	T3P, Pyridine, EtOAc, 15 mmol scale	90% isolated
6	T3P, Pyridine, EtOAc, 58 mmol scale	80% isolated

The cyclization proved to be more complex. The optimization of the procedure is summarized in **Table 28**. At first, an acid catalyzed cyclization using HCl in acetic acid was investigated. Performing the reaction at room temperature (entry 1) did not yield any product and only starting material was observed. Increasing the temperature to reflux, provided full cyclization although the product was hydrolyzed to free acid **127** (entry 2). Reducing the temperature to 65 °C reduced the rate of hydrolysis to approximately 30%. The product was isolated by crystallization from ethyl acetate/hexane mixture (entry 3) in 55% yield.

Conducting the reaction in neat acetic acid at reflux with the intention to limit the ester hydrolysis by the water present in conc. HCl did not yield any conversion of the starting material (entry 4). Similar behavior was observed when HCl was substituted for pTSA (entry 5). Acetic anhydride was then used as a dehydrative agent (entry 6), but no product was observed. Use of sulfuric acid as a dehydrative agent (entry 7) and as a strong acid catalyst yielded only sulfonated starting material. PPA (entry 8) provided full conversion, although approximately 70% of the ester was hydrolyzed into acid **127**. Using H₃PO₄ instead of PPA (entry 9) provided full conversion and limited ester hydrolysis to approx. 30%. T3P in DMF was also used as a dehydrating agent, although only low conversion was observed (entry 10).

The use of BF₃.OEt₂ in refluxing dioxane¹⁹⁴ (entry 11) provided the product in 60% yield. More careful control of the reaction temperature and ensuring the refluxing of the reaction mixture enabled full conversion of the starting material to the product. The reaction was also scaled up to 46 mmol. The product was isolated in high yields between 70-86% (entries 12-15). Last, a slight modification of the reaction workup yielded product **128** in the almost quantitative yield even at a large scale (entry 16).

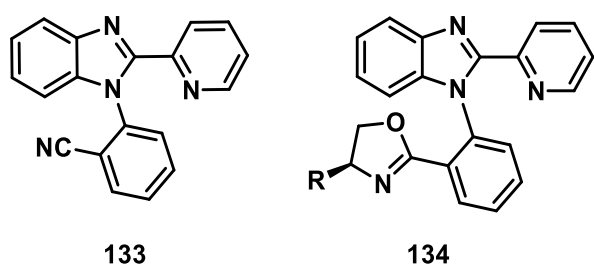
Table 28 Optimization of cyclization conditions

Entry	Conditions	Result
1	HOAc, HCl (10:1) RT	No reaction
2	HOAc, HCl (10:1) reflux	Hydrolysis to acid 127
3	HOAc, HCl (10:1) 65°C	55% isolated after recrystallization ^a
4	HOAc, 100°C	No reaction
5	pTSA, HOAc, 70°C	No reaction
6	Ac ₂ O, reflux	No reaction
7	HOAc, H ₂ SO ₄ , reflux	Sulfonated starting material observed ^a
8	PPA, 150°C	70% hydrolysis to 127
9	H ₃ PO ₄ , reflux	70% 128 , 30% hydrolysis to 127
10	T3P, DMF, RT	5% conversion ^a
11	BF ₃ .OEt ₂ , dioxane, 90°C, 0.5 mmol scale	80% conversion ^a , 60% isolated
12	BF ₃ .OEt ₂ , dioxane, reflux, 2 mmol scale	73% isolated after recrystallization
13	BF ₃ .OEt ₂ , dioxane, reflux, 11 mmol scale	77% isolated after recrystallization
14	BF ₃ .OEt ₂ , dioxane, reflux, 10 mmol scale	68% isolated after recrystallization
15	BF ₃ .OEt ₂ , dioxane, reflux, 46 mmol scale	86% isolated after recrystallization
16	BF ₃ .OEt ₂ , dioxane, reflux, 31 mmol scale	Quantitative, different workup

^a by HPLC

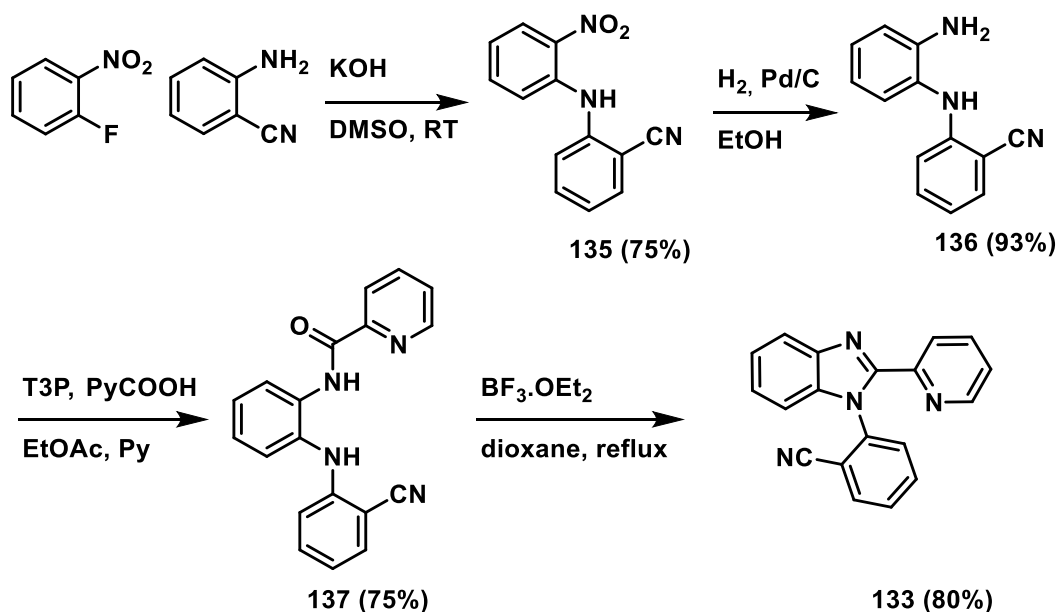
The substitution of K₂CO₃ for Na₂CO₃ in the quench of the reaction was crucial. The formed NaBF₄¹⁹⁵ is significantly more soluble in water (1080 g/L)¹⁹⁶ compared to KBF₄ (5.5 g/L)¹⁹⁶ while being less soluble in organic solvents. This allowed the precipitation of the NaBF₄ from the reaction mixture after quench and the residual NaBF₄ was removed after extraction with water. The removal of residual salts from the product, allowed for isolation of the product as a solid material compared to the oils which required purification by recrystallization (entries 12-15).

The nitrile derivative **133** was also prepared. The nitrile group would allow synthesis of various other derivatives. Most importantly, diastereomeric oxazoline **134** (**Figure 38**) could be prepared in one step from the nitrile, which would allow for separation of the atropisomers by the same method as was used for separation of TBBA.

**Figure 38** Structure of nitrile **133** and oxazoline **134**

The synthesis of **133** was similar to the synthesis of **128**. At first, 2-aminobenzonitrile was arylated with 2-fluoronitrobenzene using DMSO and KOH. The reaction proceeded well at room temperature and

product **135** was isolated by simple precipitation from water.¹⁹⁷ The nitro group was reduced using H₂ and Pd/C catalyst in EtOH and the reduced derivative **136** was acylated with pyridine-2-carboxylic acid using T3P in EtOAc/pyridine. Amide **137** was isolated in 75% yield. The BF₃·OEt₂ promoted cyclization to yield product **133** which was isolated by simple precipitation from the reaction mixture after the quench of the BF₃ (Scheme 32).

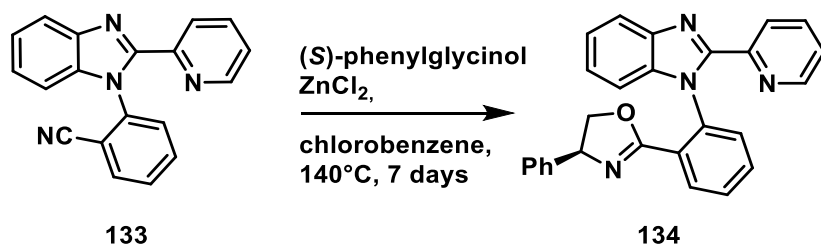


Scheme 32 Synthesis of nitrile **133**

4.3.3. Resolution of pyridine catalyst **128**

4.3.3.1 Via diastereomeric oxazolines

At first, the same procedure as in the case of TBBA was performed. The oxazoline was prepared by direct reaction of the nitrile **133** with (*S*)-phenylglycinol in the presence of ZnCl₂ in chlorobenzene at 140°C (Scheme 33).¹⁹⁸ The reaction proceeded without formation of any byproducts; however, 7 days of heating were required to fully convert nitrile **133** to oxazoline **134**. Unfortunately, diastereomers were impossible to separate on TLC or column chromatography but separation of small amounts was possible by HPLC.



Scheme 33 Synthesis of oxazoline **134**

4.3.3.2. Resolution via diastereomeric salt formation

The resolution via formation of oxazolines was possible, but only for small amounts. Therefore, further structural diversification was not possible. For this reason, the resolution of ester **128** was developed. The results are displayed in **Tables 29** and **30**.

Table 29 Resolution of **128** with LTA mix

Entry	Resolving agent	Solvent and concentration	Yield ^a	%ee
1	LTA mix ^b	EtOAc 0.75M	0	
2	LTA mix	MeOH 0.75M	37%	85%
3	LTA mix	MeOH 0.375M ^c	83%	42%
4	LTA mix	BuOH 0.6M	87%	57%
5	LTA mix	BuOH 0.375M ^c	73%	63%
6	LTA mix	ACN 0.16M	42%	85%
7	LTA mix	ACN 0.045	60%	90%
8	LTA mix	ACN 0.21	65%	67%
9	LTA mix	ACN 0.045M ^c	45%	87%
10	LTA mix	ACN 0.1M	56%	84%
11	LTA mix	ACN 0.05	54%	93%

^a Calculated from theoretical amount of the enantiomer in the starting racemate (all enantiomer isolated = 100% yield)

^b Equimolar mixture of L-dibenzoyl tartrate, L-dianisoyl tartrate and L-ditoluoyl tartrate

^c Recrystallization of the previous batch

Initially, the “Dutch resolution” procedure^{140–142,199} was used using LTA mix (L-dibenzoyl tartrate (L-DBT), L-ditoluoyl tartrate (L-DTT), and L-dianisoyl tartrate (L-DAT)). At first, the resolution was attempted in ethyl acetate and methanol (entries 1 and 2). No precipitate was observed in EtOAc, but the product was isolated in methanol in 37% yield and 85% ee. Recrystallization from MeOH reduced the enantiomeric purity (entry 3). Crystallization from BuOH provided the product in high yield; however, the enantiomeric purity was only 57% (entry 4). Recrystallization (entry 5) improved the enantiomeric purity to 63%.

Using acetonitrile as a solvent (entry 6) yielded the product in 42% yield and 85% enantiomeric purity which was slightly better compared to crystallization from MeOH. The recrystallization (entry 7) improved the enantiomeric purity to 90%. Increasing the concentration to 0.21M (entry 8) slightly improved the yield, but the enantiomeric purity dropped to 67%. Recrystallization from acetonitrile improved the enantiomeric purity to 87% (entry 9). Reducing the concentration even further to 0.1M (entry 10) yielded the product in high enantiomeric purity (84%) and 56% yield. Further dilution of the crystallization to 0.05M (entry 11) had positive effect on enantiomeric purity (93%) while the yield was same as when the more concentrated solution was crystallized (54%).

Next, because the LTA mix worked well, each of the tartaric acid derivatives were used alone to further optimize the procedure. The results are presented in **Table 30**.

Table 30 Use of acylated tartrates as a single resolving agent for resolution of **128**

Entry	Resolving agent	Solvent and concentration	Yield ^a	% ee
1	L-DBT	ACN, 0.06M	88%	77%
2	L-DTT	ACN, 0.15M	---	
3	L-DAT	ACN, 0.125M	74%	74%
4	L-DBT	MeOH 0.187M	75%	75%
5	L-DBT	ACN, 0.1M	61%	80%
6	L-DBT	ACN, 0.115M	71%	80%

^a Calculated from theoretical amount of the enantiomer in the starting racemate (all enantiomer isolated = 100% yield)

The use of L-dibenzoyl tartrate in acetonitrile (entry 1) yielded the product in high yield and enantiomeric purity. No precipitation was observed when L-ditoluoyl tartrate was used (entry 2) while the L-dianisoyl tartrate provided the product in slightly lower yield and enantiomeric purity (entry 3). Using methanol as a solvent had a negative effect for the yield although the enantiomeric purity stayed the same (entry 4). Further increase of concentration compared to entry 1 had also a negative effect on the yield although the enantiomeric purity was slightly higher (entries 5 and 6). In the end, the enantioenriched product was recrystallized although in some cases the drop of enantiomeric purity was observed. The likely cause was poor solubility of the salt in acetonitrile and required prolonged heating.

An alternative protocol was developed: the enantioenriched salt after single crystallization from acetonitrile was neutralized with NaOH and freebase **128** was crystallized from EtOAc or EtOAc/hexane mixture which yielded the product in 99%+ enantiomeric purity. This modification was then used to resolve the racemate on a gram scale. The absolute configuration of the isolated product was determined by X-Ray crystallography (**Figure 39**)

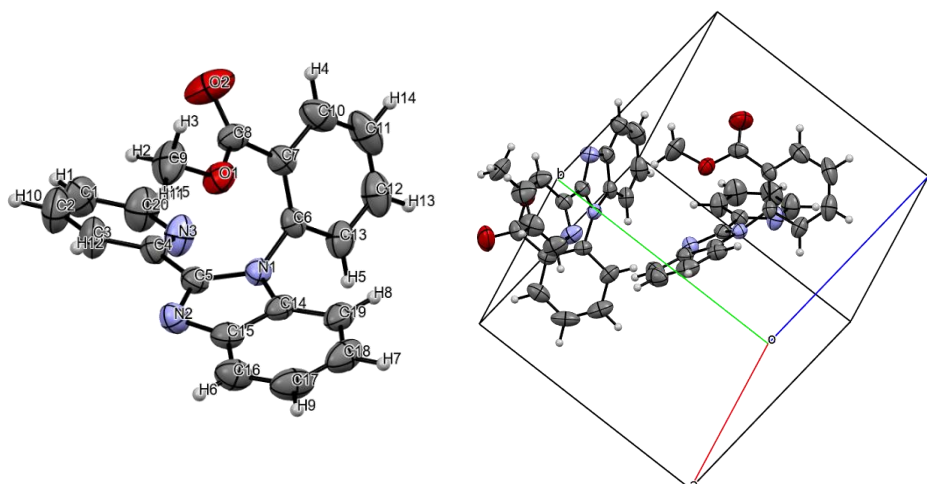
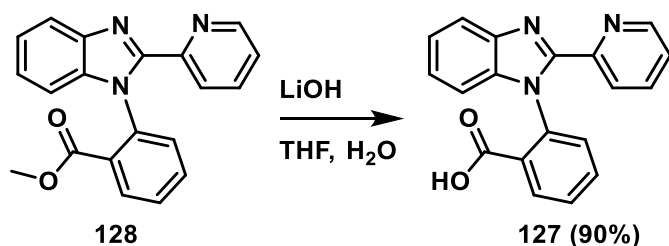


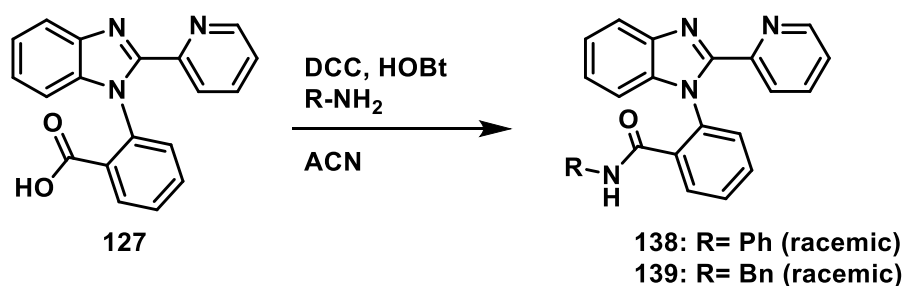
Figure 39: The molecular structure of (*P*)-**128** isolated from filtrate (see experimental part for more details) together with the atom labelling scheme. The thermal ellipsoids are drawn at the 50% probability level.

4.3.4. Modifications of the structure of the ligand 128

For further modifications, enantiopure ester **128** was hydrolyzed to acid **127** using LiOH (Scheme 34). The hydrolysis of the ester proceeded well at room temperature and the product was isolated by simple evaporation and acidification of the reaction mixture which caused a precipitation of the product. Unfortunately, the acid was found to be racemic after further derivatization to the amide **138** and **139** (Scheme 35).

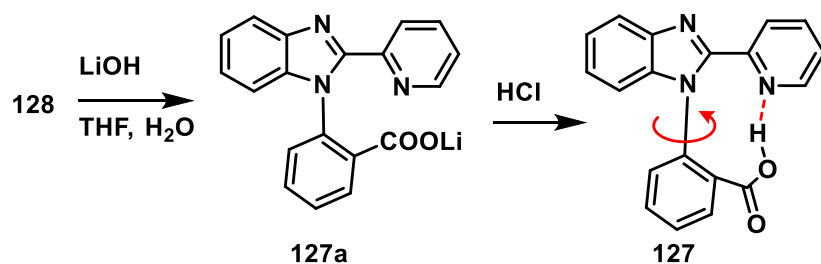


Scheme 34 Hydrolysis of ester **128**



Scheme 35 Amidation of **127**

At this time, it was not known whether the racemization occurred during the hydrolysis or during the amidation. Direct analysis of acid **127** on chiral SFC was not possible due to problematic separation of the enantiomers. For this reason, indirect analysis via the amides was used. Literature search suggested that the racemization might have occurred during the acidification of the reaction mixture by formation of a hydrogen bond between the carboxyl group and the pyridine nitrogen which lowers the rotational barrier (Scheme 36).²¹



Scheme 36 Acid promoted racemization of acid **127**

For this reason, the hydrolysis of the ester was modified, and the acidification step was omitted. Acid **127** was isolated as a lithium salt **127a** after simple evaporation of the reaction mixture. The lithium salt was then amidated using DCC, HOBt in acetonitrile to yield benzylamide **139** in good yield and reasonable enantiomeric purity (77% ee). This drop in the enantiomeric purity suggested, that the acid catalyzed racemization was a valid hypothesis, although it did not rule out the possibility of partial racemization during hydrolysis and partial racemization during the amidation.

Multiple other amides were prepared (**Figure 40**) as racemates and some were separated on preparative HPLC with chiral stationary phase by Ondřej Kurka, Ph.D. from the Department of Analytical chemistry at our university. This separation yielded enough material for reduction experiments (*vide infra*). However, due to a lack of time and COVID-19 only ligands **138** and **139** were separated. Ligands **138-142** were prepared by simple amidation using DCC/HOBt while the ligand **143** was prepared by two step synthesis. First, *ortho*-phenylene diamine was acylated with the acid **127** using DCC/HOBt and then the amide was cyclized into the benzimidazole using BF₃.OEt₂ mediated cyclization.¹⁹⁴

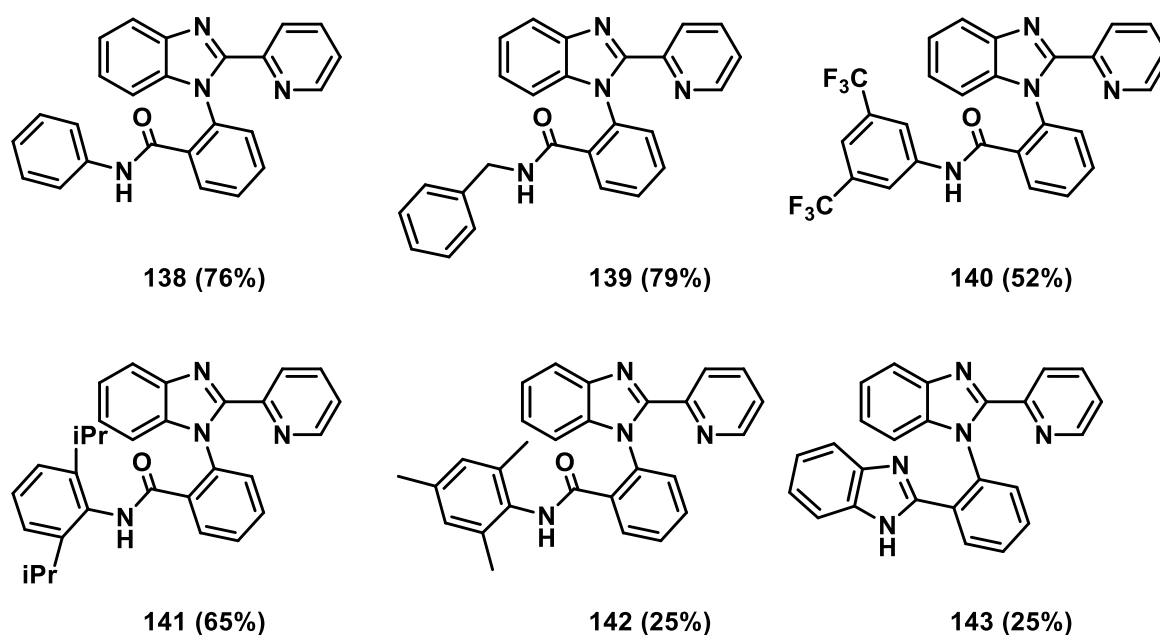
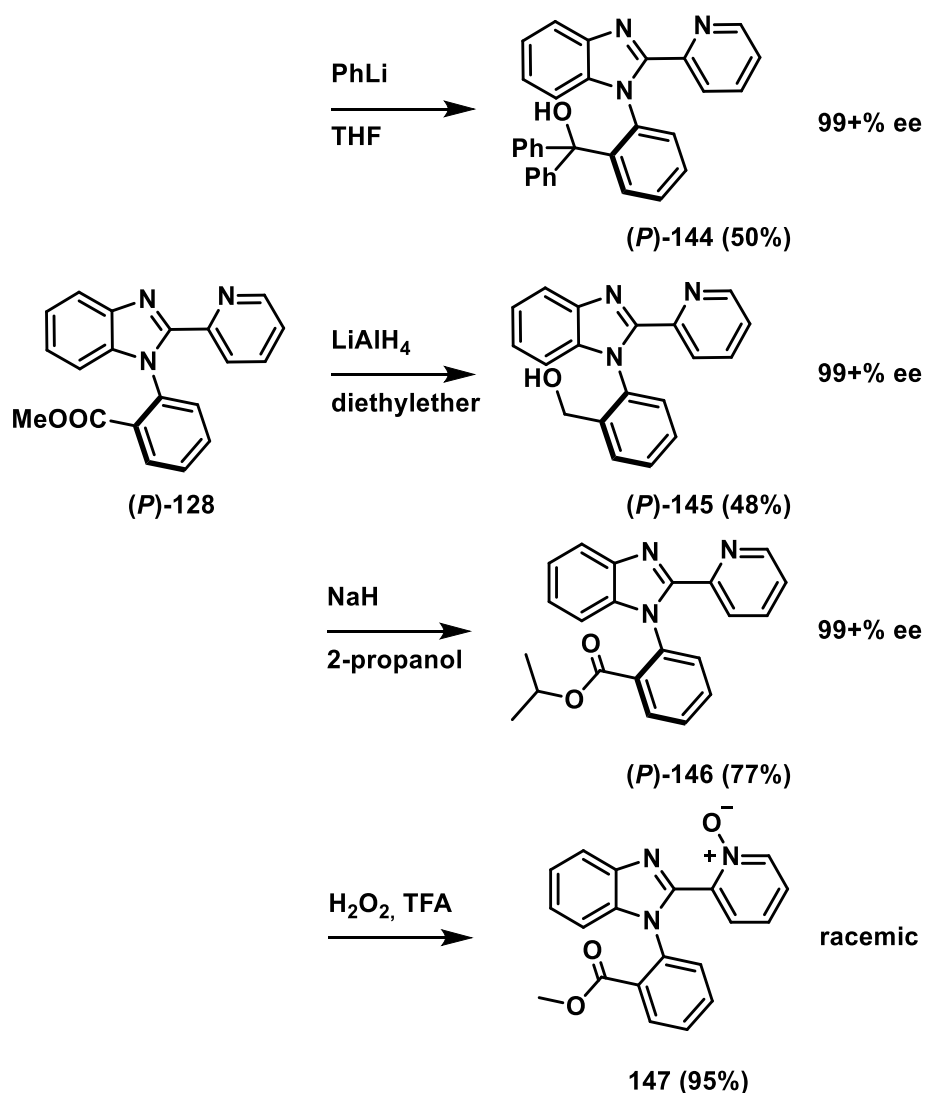


Figure 40 Prepared amide ligands

Further modifications of the structure were attempted. Addition of phenyl lithium yielded triarylmethanol derivative **144** in high yield and purity. Interestingly, no racemization was observed during this reaction (**Scheme 36**). Reduction of the methyl ester **128** with LiAlH₄ in diethyl ether provided hydroxymethyl ligand **145** with no loss of enantiomeric purity. Transesterification using NaH and isopropyl alcohol yielded ligand **146** again with no loss of enantiomeric purity. The oxidation towards the N-oxide **147** provided only racemic product. The exact mechanism of the racemization is unknown. We speculate that the possible nucleophilic attack of the N-oxide oxygen on the carbonyl followed by decomposition of the tetrahedral intermediate back to **147** with rotation around the chiral

axis. The configuration of isolated products **144-146** was based on the configuration of the starting material.

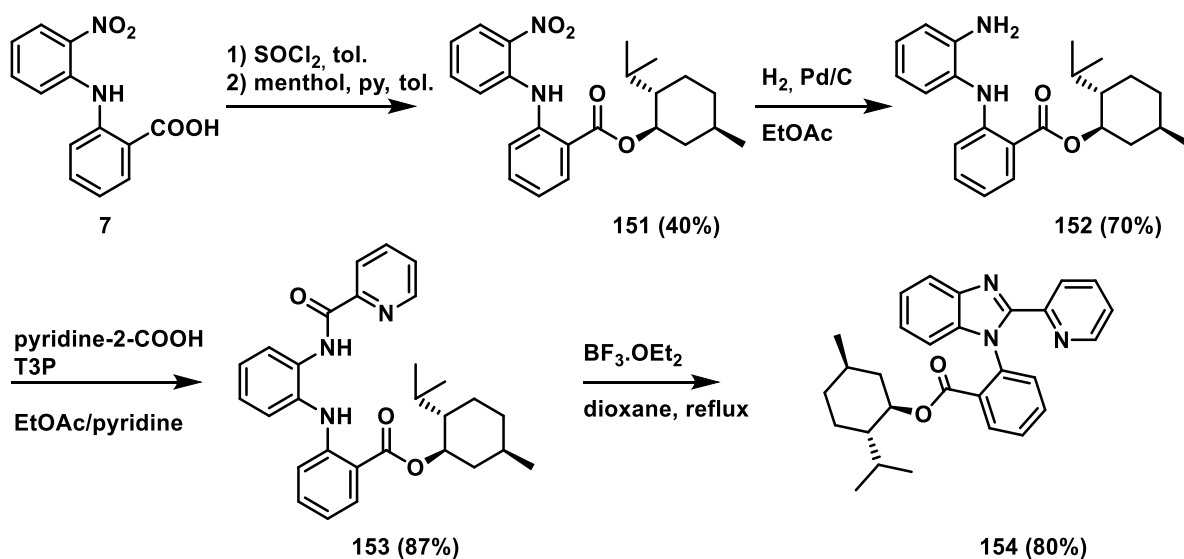


Scheme 36 Structural modifications of ligand **128**

Alternative diversification methods were explored. The synthesis of acyl azide **148** was envisioned via hydrazine derivative **149**. The azide could then act as a leaving group in amidation reactions,²⁰⁰ or it could be converted into amine via Curtius rearrangement or the intermediate isocyanide might be trapped by nucleophiles and yield variously substituted ureas. Importantly, the use of the azide as a leaving group could provide access to various amides without the need of preparation of acid **127**. Possibly, no racemization would be observed in the preparation of hydrazide **149** due to higher steric requirements compared to carboxyl anion and because no racemization was observed during transesterification to the isopropyl ester **146**

At first, the methyl ester **128** was transformed into the hydrazine derivative **149** by reaction with hydrazine hydrate in methanol. Unfortunately, partial racemization was observed and hydrazide **149** was isolated in 70% ee. (Scheme 37)

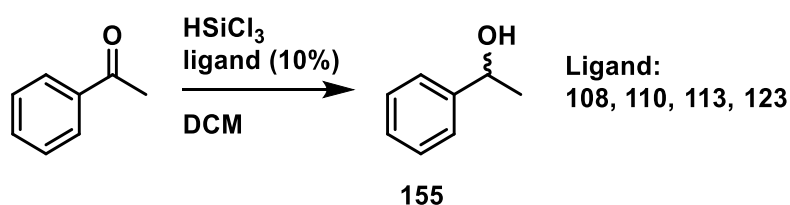
the product **154** in 80% yield. Unfortunately, separation of diastereomers was not possible and NMR analysis revealed only low levels of atroposelectivity of the products being isolated in 10:8 ratio (**Scheme 39**).



Scheme 39 Attempted atroposelective cyclization with menthol as an auxiliary

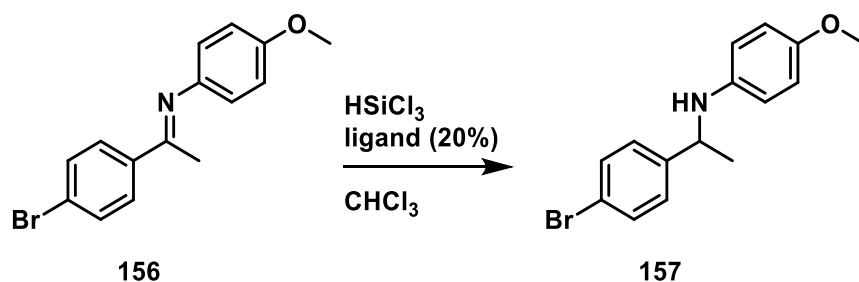
4.4. Reduction experiments

At first, reduction attempts to reduce acetophenone into 1-phenylethan-1-ol **155** failed and no conversion was observed (**Scheme 40**).



Scheme 40: Reduction of acetophenone

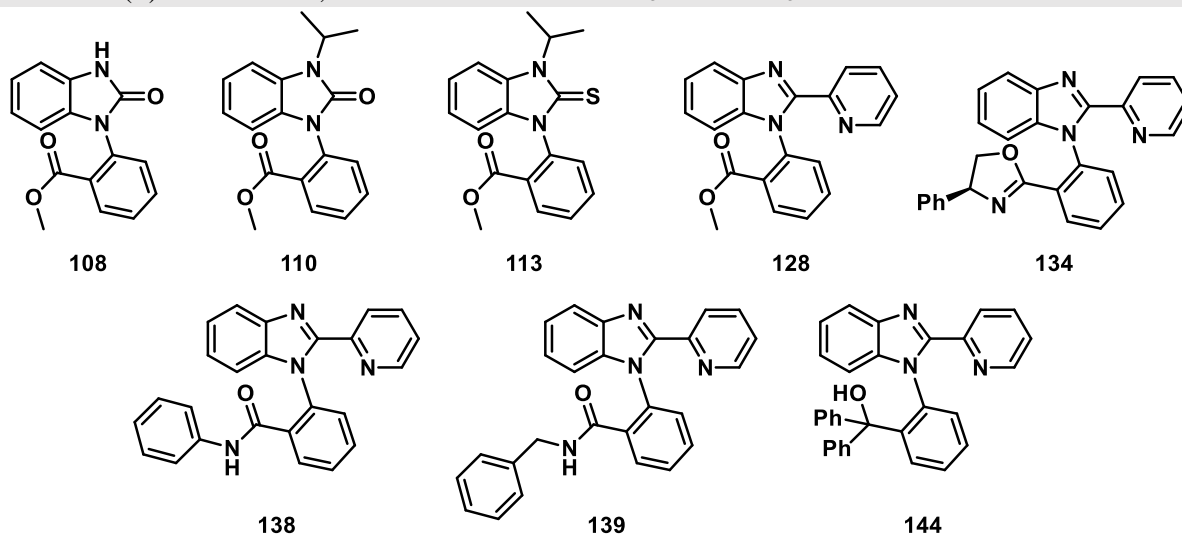
Afterwards, we turned our attention towards the reduction of imines. Imine **156** was used as a model substrate for the reduction (**Scheme 41**). Multiple ligands were evaluated, and the results are summarized in **Table 31**.



Scheme 41: Model reaction of imine reduction for ligand screening

Table 31: Ligand screening on reduction of imine **156**

Entry	Ligand	Loading (mol%)	Solvent	Er.	Yield
1	Rac-108	20	CHCl ₃	--	--
2	Rac-110	20	CHCl ₃	--	--
3	Rac-113	20	CHCl ₃	--	--
4	(P)-128	20	CHCl ₃	67/33	70%
5	(P)-134	20	CHCl ₃	65/35	65%
6	(P)-138	20	CHCl ₃	81/19	70%
7	(P)-139	20	CHCl ₃	80/20	70%
8	(P)-144	20	CHCl ₃	82/18	65%
9	(P)-128	20, TES used instead of HSiCl ₃	CHCl ₃	--	--



At first, the benzimidazole-2-on derivatives **108** and **110** (entries 1 and 2) were tested; however, no conversion of the starting material was observed. The same was observed in the case of thio analogue **113** (entry 3). Fortunately, the methyl ester **128** yielded the product in 70% yield and moderate enantioselectivity (30% ee, 65:35 er.) (Entry 4). The oxazoline ligand **134** yielded the product in a similar yield and similar enantioselectivity (entry 5). The use of anilide **138** and benzylamide **139** as a ligand, significantly improved the enantioselectivity towards 60% ee (entries 6 and 7). Similar results were obtained when triarylmethanol ligand **144** was used (entry 8). Using triethylsilane instead of trichlorosilane (entry 9) did not show any conversion of the starting material as expected. This might

likely be caused by lower electrophilicity of the silicon atom compared to the trichlorosilane. This lower electrophilicity then does not allow coordination of the ligand and formation of the active reducing agent.

Further experiments were highly complicated by the available amounts of the ligand. For this reason, we used methyl ester **128** as a model ligand for the optimization of the procedure and then the optimized conditions were used with other ligands.

At first, the reduction using 20 mol% ligand loading was reproduced (**Table 32**, entry 1). The product was isolated with similar enantiomeric purity as in the initial experiment. Reducing the ligand loading to 10% (entry 2), 5% (entry 3), or 1% (entry 4) did not have a significant impact on the enantioselectivity contrary to the expectations. Furthermore, it seemed that the reduction of the ligand loading proved to be beneficial (compare entry 1 and 4).

Table 32: Effect of ligand loading on reduction of imine **156**

Entry	Ligand	Loading (mol%)	Solvent	Er.
1	(P)-128	20	CHCl ₃	69/31
2	(P)-128	10	CHCl ₃	72/28
3	(P)-128	5	CHCl ₃	73/27
4	(P)-128	1	CHCl ₃	74/26
5	(P)-138	1	CHCl ₃	75/25
6	(P)-139	1	CHCl ₃	75/25
7	(P)-144	1	CHCl ₃	Slow reaction

The amide ligands **138** and **139** yielded the product with slightly higher enantiomeric purity compared to the 20% loading (entries 5 and 6). Last, the reduction utilizing triarylmethanol ligand **144** proceeded significantly slower and the product was not isolated (entry 7).

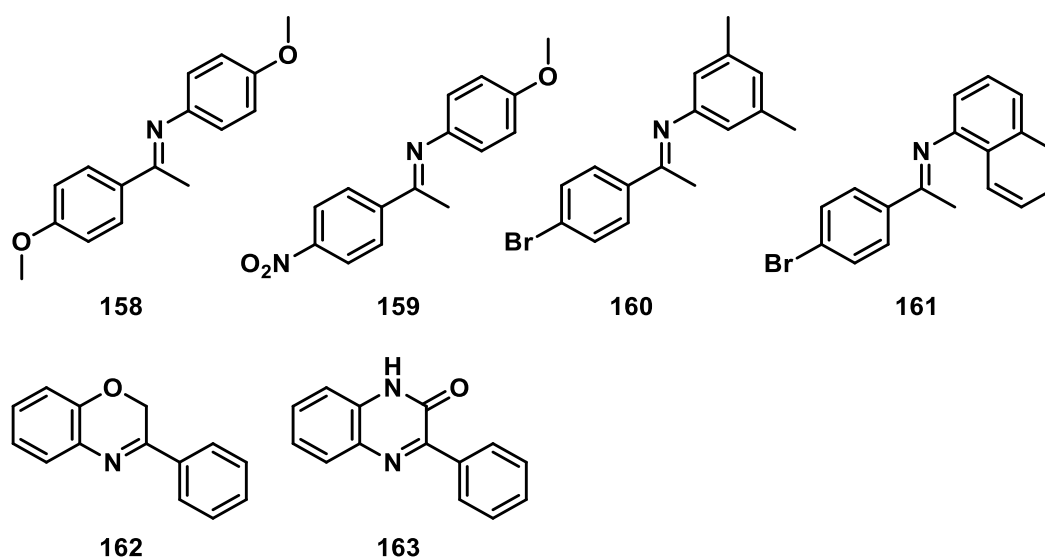
Next, the solvent effect was tested (**Table 33**). At first, the reaction was conducted in dichloromethane (entry 2). Slight improvement in the enantioselectivity was observed compared to chloroform (entry 1). Changing solvent to toluene unexpectedly improved the enantioselectivity of the reduction to 60% enantiomeric excess (85:15 enantiomeric ratio) (entry 3). Similar results were obtained after reproducing the experiment (entry 4). The expected role of π - π interactions to stabilize the transition state¹¹⁹ was not shown and quite possibly, in the case of ligands **129-136** if the interaction is present, it has negative instead of positive effect on the enantioselectivity.

Table 33: Solvent effect on reduction of imine **156**

Entry	Ligand	Loading (mol%)	Solvent	Er.
1	(P)-128	1	CHCl ₃	74/26
2	(P)-128	1	DCM	77/23
3	(P)-128	1	toluene	85/15
4	(P)-128	1	toluene	83/17
5	(P)-138	1	toluene	80/20
6	(P)-139	1	toluene	76/25
7	(P)-144	1	toluene	85/15
8	(P)-146	1	toluene	72/28
9	(P)-128	5	toluene	63/37

In the case of ligands **138** and **139** (entries 5 and 6), no improvement in enantioselectivity was observed compared to ligand **128** (entry 3) suggesting the possibility of a different transition state or different interactions playing a key role. Possibly, the amide NH might be involved in the reaction. Furthermore, similar enantioselectivity of the reaction was observed for ligand **144** (entry 7) compared to ligand **128** (entry 3). More importantly, significant improvement in the rate of the reaction was observed. Slow reaction rate was observed in chloroform (**Table 32**, entry 7). Full conversion was observed together with high enantioselectivity in toluene (**Table 33**, entry 7). Isopropyl ester **146** (entry 8) showed lower levels of enantioselectivity as the methyl ester (entry 3) and benzylamide **139** (entry 6). Last, 5 mol% of ligand **128** were used (entry 9) to confirm the positive effect of the reduced loading. The product was isolated in enantiomeric ratio 63/37 which is significantly worse compared to 1% loading (entry 1, 74/26 er)

Last, other imines **158-163** (**Figure 41**) were tested with using the optimized conditions (1 mol% of ligand, toluene, RT).

**Figure 41:** Structures of prepared imines

The results are summarized in **Table 34**. The reduction of the dimethoxyimine **158** yielded the resulting amine in 60% yield and moderate enantioselectivity (er. 73/27) (entry 1). The reduction of the nitro-methoxy derivative **159** proceed in similar manner with moderate enantioselectivity (er. 78/22) and yield 65% (entry 2). Unfortunately, only decomposition to the acetophenone and aniline was observed in the case of compounds **160** and **161**. The exact cause is unknown since the reaction was also attempted in dry solvents with molecular sieves. Possibly, the higher steric hinderance on the aniline part plays a role. Last, the cyclic imines **162** and **163** were reduced. The imine **162** was reduced with low enantioselectivity (er. 65/35) (entry 5). The reduction of imine **163** did not proceed, possibly due to the low solubility of the imine in toluene. Further addition of chloroform to dissolve the starting material did not have significant effect and no conversion was observed (entry 6).

Table 34: Reduction of imines under optimized conditions with (**P**)-**128**

Entry	Imine	Er.	Yield
1	158	73/27	60 %
2	159	78/22	65 %
3	160	Decomposition	
4	161	Decomposition	
5	162	65/35	70 %
6	163	No reaction	

4.4.1. Nonlinear effect

Preliminary experiments were conducted to get some insight into the reaction mechanism and transition state. At first, results in **Table 32** (lowering the loading of ligand increases the enantiomeric purity of the product) indicate that only one molecule of the ligand is likely involved in the transition state. Further experiments with variable enantiomeric purity of ligand **128** were performed (**Table 35**). At first, the reductions with racemic (entry 1) and enantiopure ligand **128** (entry 7) were conducted. Further, lowering the enantiomeric purity of the ligand, caused variation of the enantiomeric purity of the product (entries 2-6).

Table 35: Study of nonlinear effect with ligand **128**

entry	%Ee ligand (1 mol%)	%Ee product 157
1	0	0
2	19.5	10
3	32.5	13
4	45	21
5	65	10
6	78	17
7	97	67

As can be seen in **Figure 42**, there is a clear nonlinear relationship (NLE) between the enantiomeric purity of the ligand and enantiomeric purity of the product. This negative nonlinear effect ((-)-NLE)^{202,203} suggests more than one molecule of the ligand is involved in the transition state.²⁰² This is in direct contradiction with previous results with lower ligand loadings providing higher %ee. Possibly, two competing processes are occurring at the same time: a) coordination of a single molecule of the ligand to HSiCl₃ which further provides product with higher %ee and b) coordination of two molecules of the ligand to HSiCl₃ which also forms catalytically active species; however, reaction catalyzed by these species provide a product with lower %ee. Those two competing processes could explain the unusual local minimum in the %ee product vs %ee ligand dependency (**Figure 42**)

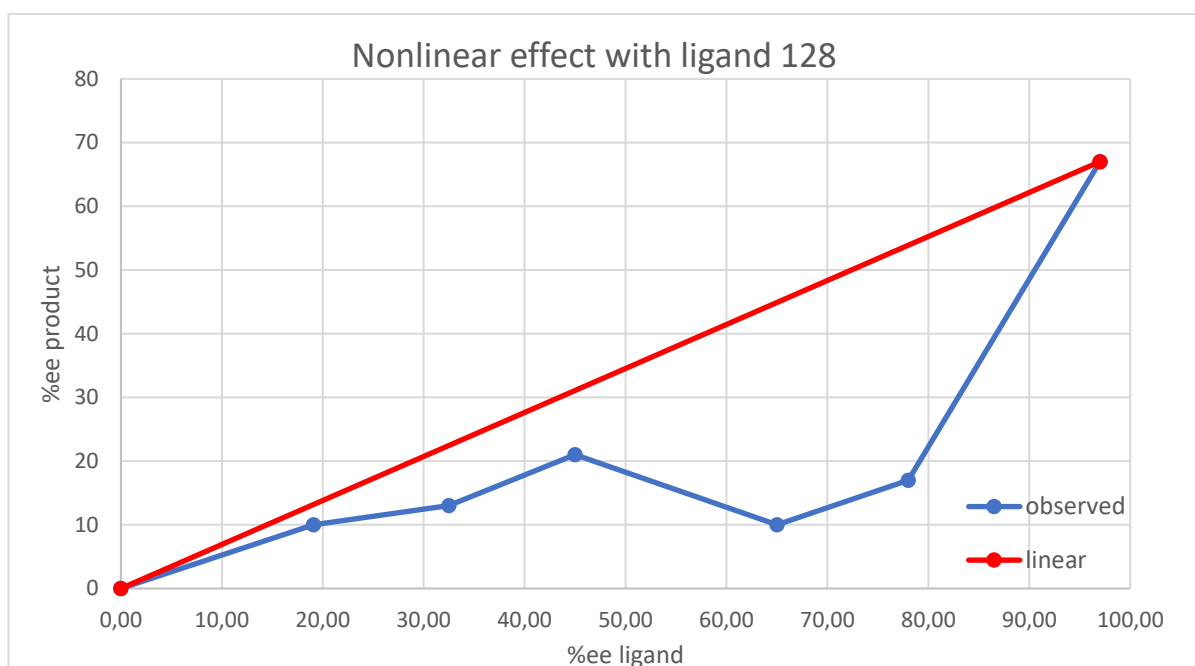


Figure 42: Nonlinear effect of imine reduction with ligand **128**

The magnitude of the NLE highly depends on the specific conditions of the reaction such as temperature, concentration, loading of the ligand etc.; therefore, these presented results shall be considered only preliminary and indicate much more complicated kinetic of the reduction mechanism. Furthermore, due to the extremely low loading of the ligand and scale of the reaction, the experiment might be tainted by higher error due to the required manipulations.

Compared to the literature examples, the presented ligands provide lower enantioselectivity. Most of the examples found in literature provided products with higher enantioselectivity er. 90/10 (80%ee) or higher.^{119,120,125,204,205} Further structural optimization and modifications are required to improve the enantiomeric excess of the product to already known ligands.

5. Conclusion

In conclusion, this thesis deals with two projects. At first, novel chiral derivatization agent, 2-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-1-yl)benzoic acid (TBBA) was developed for the assignment of the absolute configuration of chiral alcohols and amines. Racemic TBBA was prepared by the conventional methods and subsequent chiral resolution was carried out *via* conversion into a diastereomeric pair of oxazolines. Atroposelective synthesis of TBBA was attempted as well but only with partial success.

Eighteen chiral secondary alcohols and α -chiral primary amines with the known absolute configuration were used to evaluate TBBA. All model compounds followed the proposed general conformational model for assignment of absolute configuration.

Furthermore, eighteen β -chiral primary alcohols and amines with the known absolute configuration were tested as well. Seventeen of them fully followed the devised conformational model while one, (*S*)-*N*-Boc-Phenylglycinol, offered the opposite absolute configuration.

Further investigation of this irregularity involved synthesis of six other Boc-protected amino alcohol derivatives and eight (*S*)-phenylglycinols to probe limitations of TBBA. Synthesis of multiple *N*-substituted derivatives revealed strong influence of the *N*-carbonyl functionality. Hydrogen bond was revealed by B3LYP-G-31* and ω B97X-D/6-31G* in silico modelling. The hydrogen bond was further confirmed by ¹H experiments in acetone-D₆ which acts as an H-bond acceptor. Significant differences in the $\Delta\delta^{PM}$ were observed in acetone-D₆ compared to CDCl₃. The influence of the hydrogen bond is further increased by the presence of *N*-carbonyl moiety due to the repulsion between CF₃ and carbonyl oxygen.

The aim of the second project was to develop novel axially chiral ligands for asymmetric reduction of imines using HSiCl₃ as a cheap hydride source. 2-(2-Pyridyl)benzimidazole-based ligand was prepared and resolved into enantiomers on a multigram scale. Other structural modifications were attempted; however, racemization was observed in the case of acylation reaction. New ligands were prepared as racemates and some of them were resolved by chiral semipreparative HPLC. Unfortunately, external reasons did not allow for resolution of all prepared racemates.

Several reduction experiments were performed and revealed methyl 2-(2-(pyridin-2-yl)-1*H*-benzo[*d*]imidazol-1-yl)benzoate as the best ligand when used in toluene at low catalytic loadings. Multiple imines were reduced in moderate enantioselectivity, and preliminary experiments revealed a possible negative nonlinear effect observed on a model substrate. Some of the prepared imines were not reduced due to their poor solubility in toluene. This project remained unfinished due to time reasons.

6. Experimental part

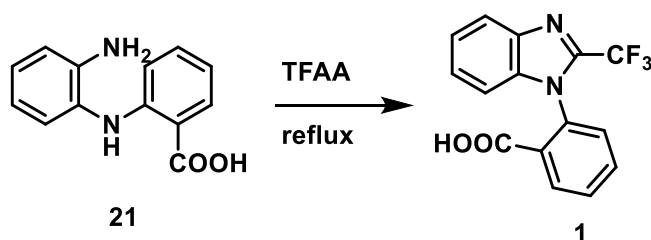
GENERAL METHODS: All reactions were carried out under normal conditions without any specific precautions to exclude moisture or air from the reaction unless otherwise stated. Reaction workup and column chromatography were performed with commercial grade solvents without further purification. ^1H NMR, ^{13}C NMR, and ^{19}F NMR spectra were measured on a Jeol ECA400II (400 MHz) or Jeol ECX-500SS (500 MHz) instrument in CDCl_3 , $\text{DMSO-}D_6$ or $\text{acetone-}D_6$ as a solvent. ^1H and ^{13}C spectra were calibrated using residual nondeuterated solvent as an internal reference (7.26 and 77.16 ppm for CDCl_3 , 2.50 and 39.52 ppm for $\text{DMSO-}D_6$, 2.050 and 29.840 for $\text{acetone-}D_6$). ^{19}F spectra were calibrated by the addition of CFCl_3 as an internal reference ($\delta = 0.0$ ppm). All ^{13}C NMR spectra were measured with broadband ^1H decoupling. ^1H NMR data are reported as follows: δ , chemical shift; coupling constants (J are given in hertz, Hz) and integration. Abbreviations to denote the multiplicity of a signal were s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), app (appears as) and br (broad).

Analytical thin-layer chromatography (TLC) was performed using Kieselgel 60 F_{254} plates (Merck). Compounds were detected by UV light (255 nm) and then by basic KMnO_4 solution. Flash chromatography was performed using silica gel (35–70 μm particle size). HRMS analysis was performed using an LC-MS Orbitrap Elite high-resolution mass spectrometer with electrospray ionization (Dionex Ultimate 3000, Thermo Exactive plus, MA, USA). The samples were dissolved in MeOH or acetonitrile and injected to the mass spectrometer over autosampler after HPLC separation: precolumn Phenomenex Gemini (C18, 50 \times 2 mm, 2.6 μm), mobile phase isocratic MeOH/water/ HCOOH 95:5:0.1.

SFC chiral analyses were performed using an Acquity UPC² system (Waters) consisting of a binary solvent manager, sample manager, column manager, column heater, convergence manager, PDA detector 2998, QDa mass detector and chiral analytical columns (4.6 mm \times 100 mm, 3 μm particle size). The chromatographic runs were performed at a flow rate of 2.2 mL/min, column temperature of 38 $^\circ\text{C}$, and ABPR 2000 psi.

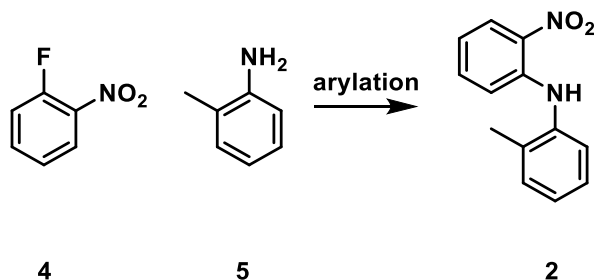
Dry solvents (THF, diethyl ether, DMF, DCM, ethanol) were dried over activated alumina and used as received from solvent purification system. Toluene was dried over activated molecular sieved or used as received from supplier. Acetonitrile was dried over activated molecular sieves.

2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoic acid (**1**)



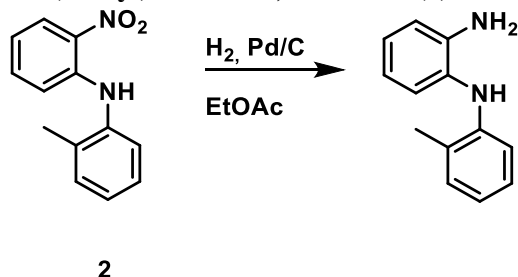
To 2-((2-aminophenyl)amino)benzoic acid **21** (11.4 g, 49.9 mmol, 1 eq.) trifluoroacetic anhydride was added (100 mL, $c = 0.5$ mmol/mL). After effervescence ended, a solution was refluxed for 70 minutes. The reaction mixture was then cooled to room temperature and added dropwise into ice-cold water (2.7 L) with rapid stirring by overhead stirrer. A white precipitate was collected by filtration and dried in vacuum at 90°C. Yield 14.5 g (94%), a pale-yellow solid. $^1\text{H NMR}$ (400 MHz, DMSO- D_6) δ 13.19 (d, $J = 84.5$ Hz, 1H), 8.18 (dd, $J = 7.7, 1.6$ Hz, 1H), 7.92 – 7.89 (m, 1H), 7.88 (dd, $J = 7.6, 1.7$ Hz, 1H), 7.81 (td, $J = 7.6, 1.3$ Hz, 1H), 7.74 (dd, $J = 7.7, 0.8$ Hz, 1H), 7.44 – 7.38 (m, 2H), 7.06 – 7.02 (m, 1H). $^{13}\text{C NMR}$ $\{^1\text{H}\}$ (101 MHz, DMSO- D_6) δ 165.21, 140.19, 139.98 (q, $J = 38.9$ Hz), 137.36, 133.78, 133.27, 131.88, 130.94, 130.18, 129.36, 125.97, 123.72, 120.79, 118.84 (q, $J = 272.2$ Hz), 111.13. $^{19}\text{F NMR}$ (376 MHz, DMSO- D_6) δ -60.52, HRMS ESI[M+H] $^+$ calculated for $\text{C}_{15}\text{H}_{10}\text{O}_2\text{N}_2\text{F}_3+\text{H}$: 307.0689, found: 307.0685, Mp: 218-220°C

2-methyl-N-(2-nitrophenyl)aniline (**2**)



O-Toluidine (825 μL , 7.5 mmol, 1 eq), 2-fluoronitrobenzene (755 μL mmol, 1eq) and trimethylamine (1 mL, 10 mmol, 1.3 eq) were heated without solvent in pressure tube at 150°C for 20 hours. After 20 hours, the mixture was cooled to room temperature and poured into MeOH (10 mL). This mixture was cooled in ice bath and the precipitate was collected by filtration. Isolated 3.11 g (60%). $^1\text{H NMR}$ (400 MHz, DMSO- d_6) δ 9.34 (s, 3H), 8.13 (dd, $J = 8.6, 1.6$ Hz, 3H), 7.45 (dddd, $J = 8.6, 6.9, 1.6, 0.5$ Hz, 5H), 7.40 – 7.35 (m, 6H), 7.31 – 7.22 (m, 11H), 6.80 (ddd, $J = 8.4, 6.9, 1.3$ Hz, 3H), 6.67 (dd, $J = 8.7, 1.2$ Hz, 4H), 2.18 (s, 3H). $^{13}\text{C NMR}$ $\{^1\text{H}\}$ (101 MHz, DMSO- D_6) δ 143.3, 137.2, 136.3, 134.4, 132.1, 131.2, 127.1, 126.7, 126.7, 126.2, 117.0, 115.8, 17.5.

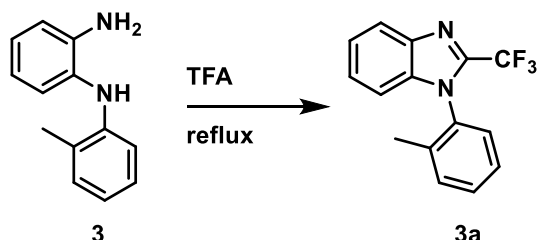
*N*1-(*o*-tolyl)benzene-1,2-diamine (**3**)



Three-necked flask fitted with stir bar, rubber septa and valve was charged with 170 mg of 10% Pd/C (0.164 mmol, 0.025 eq). **2** (1.5 g, 6.57 mmol, 1 eq) was added followed by EtOAc (30 mL). The last open neck was fitted with rubber balloon and the whole apparatus was purged with argon / vacuum cycle three times. After the evacuation of the flask, hydrogen gas was introduced, and the suspension was

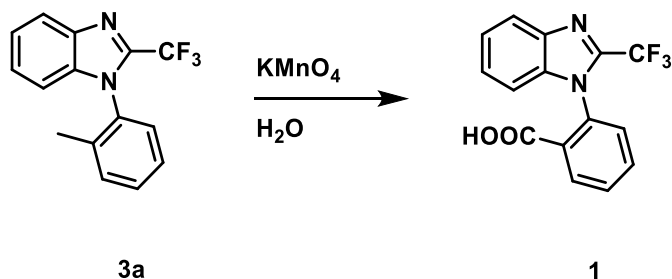
rapidly stirred at room temperature for 22 hours. After 22 hours, the flask was opened to air, the suspension was filtered through pad of silica and the filtrate was evaporated yielding 1.22 g (95%) of oil which solidified by standing on air. $^1\text{H NMR}$ (400 MHz, DMSO) δ 7.07 (d, $J = 7.2$ Hz, 1H), 6.95 (t, $J = 7.8$ Hz, 1H), 6.86 – 6.77 (m, 2H), 6.73 (d, $J = 7.7$ Hz, 1H), 6.67 (dd, $J = 8.5, 6.6$ Hz, 1H), 6.58 – 6.49 (m, 1H), 6.47 (d, $J = 8.2$ Hz, 1H), 6.32 (s, 1H), 4.72 (s, 2H), 2.21 (s, 3H). $^{13}\text{C NMR}$ $\{^1\text{H}\}$ (101 MHz, DMSO) δ 143.9, 142.3, 130.3, 128.3, 126.4, 125.0, 124.0, 123.6, 118.6, 116.6, 115.1, 114.6, 17.9.

1-(*o*-tolyl)-2-(trifluoromethyl)-1*H*-benzo[*d*]imidazole (3a)



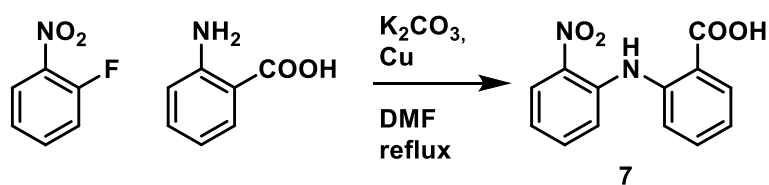
3 (600 mg, 3 mmol, 1 eq) was dissolved in TFA (6 mL) and refluxed for 18 hours. After 18 hours, the reaction was cooled to room temperature and the TFA was evaporated. The oily residue was dissolved in DCM (20 mL) and washed with 10% aq. K_2CO_3 (3x 20 mL). The organic layer was dried with MgSO_4 and evaporated to yield 400 mg of oil (65%). $^1\text{H NMR}$ (400 MHz, DMSO- d_6) δ 7.95 (dt, $J = 4.9, 3.0$ Hz, 1H), 7.61 – 7.50 (m, 3H), 7.49 – 7.41 (m, 3H), 7.07 – 7.01 (m, 1H), 1.88 (s, 3H). $^{13}\text{C NMR}$ $\{^1\text{H}\}$ (101 MHz, DMSO- D_6) δ 140.2, 139.58 (q, $J = 38.6$ Hz), 136.3, 135.8, 132.6, 131.3, 130.6, 128.6, 127.4, 126.3, 124.1, 121.2, 118.73 (q, $J = 273.7$ Hz), 111.3, 16.4. $^{19}\text{F NMR}$ (376 MHz, DMSO- D_6) δ -60.8.

Oxidation of 3a to 1



3a (400 mg, 1.45 mmol, 1 eq) was suspended in water (50 mL), KMnO_4 (1420 mg, 9 mmol, 6eq) was added and the reaction was refluxed for 24 hours. After 24 hours, HPLC analysis revealed incomplete conversion therefore KMnO_4 (1400 mg, 9 mmol, 6eq) was added and the reaction was further refluxed for 24 hours. The reaction was then cooled to room temperature and extracted with DCM (3x 50 mL). The DCM extracts were combined and washed with water (3x 50) and 10% NaOH (3x 50). The alkaline extracts were combined, acidified with conc. HCl, extracted with DCM (3x 50) and the organic extracts were combined, dried with MgSO_4 and evaporated to yield 150 mg of **1** as an oil (30%).

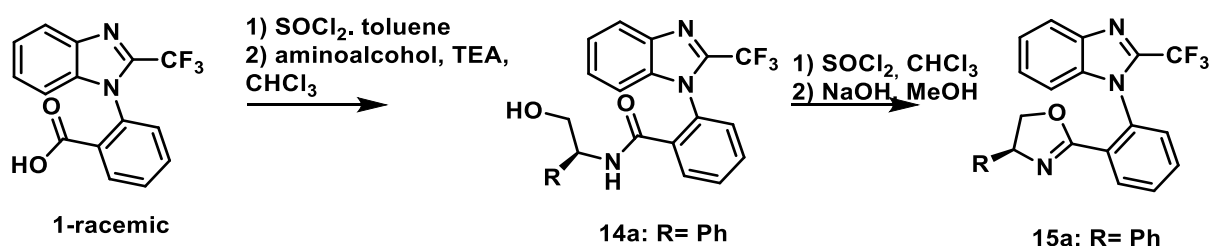
2-((2-nitrophenyl)amino)benzoic acid (7)



Anthranilic acid (16.8 g; 120 mmol) was dissolved in DMF (30 mL). 2-fluoronitrobenzene (12.75 mL; 120 mmol, 1eq), K_2CO_3 (16.5 g; 120 mmol; 1 eq) and copper (160 mg; 0.8 mmol, 0.02 eq) were added

respectively. The suspension was refluxed for 17 hrs. After 17 hours, the reaction mixture was cooled down to room temperature. The formed muddy solid was suspended in cold water (150 ml). This suspension was acidified using glacial acetic acid (150 mL). The precipitated solid was broken down into suspension using sonification and spatula until fine suspension was formed. This suspension was filtered and washed with water. The solid was then recrystallized from glacial acetic acid (125 mL), filtered, washed thoroughly with water, and dried in oven (90 °C). Yield: 22g (70%), brown solid. $^1\text{H NMR}$ (400 MHz, DMSO- D_6) δ 13.46 (s, 1H), 11.11 (s, 1H), 8.13 (dd, J = 8.4, 1.4 Hz, 1H), 8.00 – 7.95 (m, 1H), 7.67 – 7.58 (m, 2H), 7.56 – 7.49 (m, 2H), 7.13 – 7.05 (m, 2H). $^{13}\text{C NMR}$ $\{^1\text{H}\}$ (101 MHz, DMSO- D_6) δ 168.76, 142.12, 138.11, 137.20, 135.48, 133.65, 131.80, 126.31, 121.67, 120.66, 119.20, 118.60, 118.27. **HRMS** ESI[M+H] $^+$ calculated for $\text{C}_{13}\text{H}_{11}\text{O}_4\text{N}_2$: 259.0713, found: 259.0712 **Mp**: 218–221°C.

(*P/M*)-(S)-4-Phenyl-2-(2-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-1-yl)phenyl)-4,5-dihydrooxazole (*P/M*-15a)



Racemic 2-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-1-yl)benzoic acid **rac-1** (1.8 g, 6 mmol, 1 eq.) was suspended in toluene (90 mL) and SOCl_2 (2.2 mL, 30 mmol, 5 eq.) was added. A mixture was refluxed for 20 minutes (all solids dissolved). After cooling to RT, the solvent was evaporated yielding a dark oily residue. This residue was twice dissolved in CHCl_3 (25 mL) and evaporated to remove all residual SOCl_2 .

The resulting oil was dissolved in CHCl_3 (25 mL) and after cooling to 5°C (ice/water bath), a solution was added dropwise into a cooled solution of (*S*)-(+)-phenylglycinol (904 mg, 6.6 mmol, 1.1 eq.) and triethylamine (910 μL , 6.6 mmol, 1.1 eq.) in CHCl_3 (12 mL). This mixture was stirred on an ice bath for 90 min. After 90 min., the solution was washed with 10% (v/v) aq. HCl (2 x 30 mL) and 10% (m/m) aq. K_2CO_3 (2 x 30 mL) and dried over MgSO_4 .

Afterwards, the drying agent was removed by filtration and SOCl_2 (2.2 mL, 30 mmol, 5 eq.) was added to the filtrate. The solution was stirred at room temperature in an open flask for 90 minutes (monitored by TLC, hexane: EtOAc 2:1; R $_f$ = 0.75). After the reaction was completed, the solution was evaporated, dissolved in CHCl_3 , and evaporated again to yield a dark oily residue.

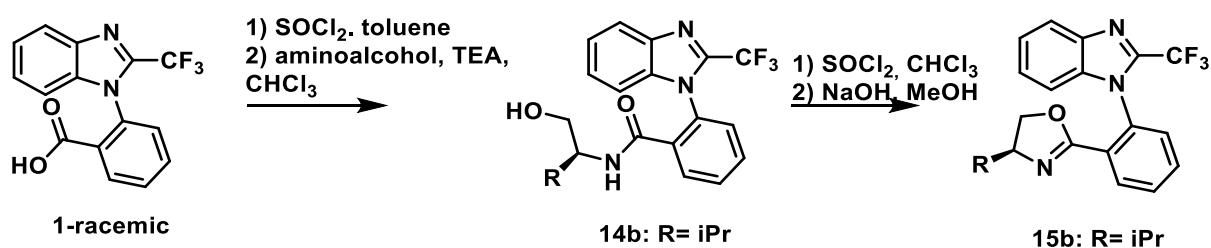
This residue was dissolved in MeOH (32 mL) and solution of NaOH (1.2 g, 30 mmol, 5 eq.) in water (12 mL) was added dropwise and the reaction was stirred for 2 hrs. (monitored by TLC, hexane: EtOAc 2:1, R $_f$ = 0.62 or Hex: EtOAc 5:1, R $_f$ = 0.32 and 0.22). After completion of the reaction, methanol was evaporated using RVO and H_2O (50 mL) was added. A cloudy solution was extracted with CHCl_3 (50 and 2x 30 mL). Organic layers were combined and dried over MgSO_4 and evaporated to yield 1.94 g of an oily mixture of diastereomers. The mixture was purified by column chromatography (10x6 cm, petroleum ether: ethyl acetate 6:1) yielding 807 mg (65% from rac. acid) of (*P*)-**15a** and 676 mg (55% from rac. acid) of (*M*)-**15** as yellow oils.

(*P*)-**15** $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.24 (dd, J = 7.6, 1.9 Hz, 1H), 7.90 (d, J = 7.3 Hz, 1H), 7.76 – 7.65 (m, 2H), 7.54 (dd, J = 7.4, 1.3 Hz, 1H), 7.43 – 7.33 (m, 2H), 7.16 – 7.08 (m, 3H), 7.02 (dd, J = 7.3, 1.2 Hz, 1H), 6.63 (td, J = 7.4, 3.2 Hz, 2H), 5.06 (dd, J = 9.9, 9.1 Hz, 1H), 4.28 (dd, J = 10.3, 8.4 Hz, 1H), 3.83 (t, J = 8.6 Hz, 1H). $^{13}\text{C NMR}$ $\{^1\text{H}\}$ (101 MHz, CDCl_3) δ 161.23 (s), 141.67 (s), 141.49 (q, J = 40.7 Hz), 141.03 (s), 137.61 (s), 133.58 (s), 132.35 (s), 131.58 (s), 130.47 (s), 129.95 (s), 128.57 (s),

127.29 (s), 126.62 (s), 126.17 (s), 125.64 (s), 123.74 (s), 121.51 (s), 119.05 (q, $J = 271.7$ Hz), 110.96 (s), 74.36 (s), 69.74 (s). ^{19}F NMR (376 MHz, CDCl_3) δ -61.52 (s). HRMS ESI[M+H] $^+$ calculated for $\text{C}_{23}\text{H}_{16}\text{ON}_3\text{F}_3+\text{H}$: 408.1318, found: 408.1320 $[\alpha]_D^{26} = -82.31^\circ$ ($c = 0.39$ MeOH).

(*M*)-**15** ^1H NMR (400 MHz, CDCl_3) δ 8.22 (dd, $J = 7.7, 1.7$ Hz, 1H), 7.95 – 7.89 (m, 1H), 7.77 – 7.65 (m, 2H), 7.53 (dd, $J = 7.6, 1.2$ Hz, 1H), 7.43 – 7.33 (m, 2H), 7.25 – 7.18 (m, 3H), 7.08 – 7.02 (m, 1H), 6.88 – 6.82 (m, 2H), 5.02 (t, $J = 9.4$ Hz, 1H), 4.40 (dd, $J = 10.2, 8.5$ Hz, 1H), 3.50 (t, $J = 8.7$ Hz, 1H). ^{13}C NMR $\{^1\text{H}\}$ (101 MHz, CDCl_3) δ 162.29 (s), 141.52 (q, $J = 39.9$ Hz), 141.33 (s), 140.86 (s), 137.66 (s), 133.40 (s), 132.41 (s), 131.87 (s), 130.46 (s), 129.68 (s), 128.67 (s), 127.66 (s), 127.07 (s), 126.68 (s), 125.77 (s), 123.88 (s), 121.50 (s), 119.00 (q, $J = 272.1$ Hz), 111.08 (s), 75.02 (s), 69.84 (s). ^{19}F NMR (376 MHz, CDCl_3) δ -61.34 (s). HRMS ESI[M+H] $^+$ calculated for $\text{C}_{23}\text{H}_{16}\text{ON}_3\text{F}_3+\text{H}$: 408.1318, found: 408.1323 $[\alpha]_D^{26} = +82.50^\circ$ ($c = 0.44$ MeOH).

(*P/M*)-4-isopropyl-2-(2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)phenyl)-4,5-dihydrooxazole (*P/M*-15b)



Racemic 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoic acid **rac-1** (150 mg, 0.5 mmol, 1 eq.) was suspended in toluene (8 mL) and SOCl_2 (0.24 mL, 2 mmol, 4 eq.) was added. A mixture was refluxed for 20 minutes (all solids dissolved). After cooling to RT, the solvent was evaporated yielding a dark oily residue. This residue was twice dissolved in CHCl_3 (25 mL) and evaporated to remove all residual SOCl_2 .

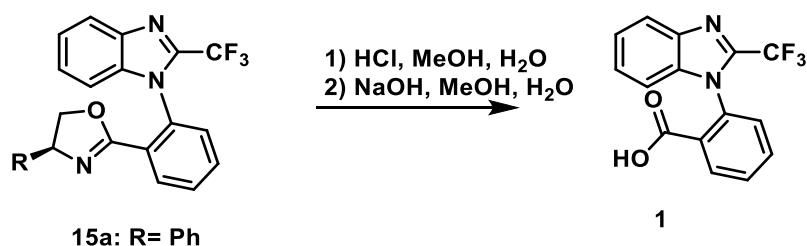
The resulting oil was dissolved in CHCl_3 (2 mL) and after cooling to 5°C (ice/water bath), a solution was added dropwise into a cooled solution of (*S*)-(+)-valinol (103 mg, 1 mmol, 2 eq.) and triethylamine (73 μL , 1 mmol, 2 eq.) in CHCl_3 (2 mL). This mixture was stirred on an ice bath for 90 min. After 90 min., the solution was washed with 10% (v/v) aq. HCl (2 x 5 mL) and 10% (m/m) aq. K_2CO_3 (2 x 5 mL) and dried over MgSO_4 to yield 174 mg of oil (87%)

This oil was dissolved in CHCl_3 (3 mL) followed by dropwise addition of SOCl_2 (146 μL , 2 mmol, 4 eq.) and the reaction was stirred open to air for 90 minutes when TLC (Hex: EtOAc 2:1) revealed consumption of the starting material. The reaction mixture was evaporated to dryness and the residue was dissolved in MeOH (2 mL) and H_2O (1 mL) and solid KOH was added (60 mg, 1 mmol, 2 eq.) and the cloudy reaction was stirred at RT. After 30 minutes 30% aq. KOH (100 μL , 1 eq.) was added together with MeOH (2 mL), the mixture become clear and was stirred at room temperature overnight. Afterwards, the reaction was diluted with water (5 mL) and extracted into CHCl_3 (3 x 10 mL) and purified by column chromatography (Hex: EtOAc 7:1) to yield two pure products:

Product 1: (20 mg, 23%): ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.07 (dd, $J = 7.5, 1.9$ Hz, 1H), 7.87 – 7.78 (m, 3H), 7.76 (dd, $J = 7.4, 1.7$ Hz, 1H), 7.36 (tt, $J = 7.3, 5.6$ Hz, 2H), 6.98 – 6.90 (m, 1H), 4.10 (dd, $J = 9.6, 8.2$ Hz, 1H), 3.72 (t, $J = 8.2$ Hz, 1H), 3.66 (dd, $J = 9.4, 6.2$ Hz, 1H), 0.97 (h, $J = 6.7$ Hz, 1H), 0.39 (d, $J = 6.7$ Hz, 3H), 0.21 (d, $J = 6.7$ Hz, 3H).

Product 2: (20 mg, 23%): ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.09 – 8.01 (m, 1H), 7.89 – 7.85 (m, 1H), 7.85 – 7.77 (m, 2H), 7.77 – 7.73 (m, 1H), 7.42 – 7.33 (m, 2H), 7.01 – 6.94 (m, 1H), 4.16 – 4.10 (m, 3H), 1.29 (h, $J = 6.7$ Hz, 1H), 0.58 (d, $J = 6.8$ Hz, 3H), 0.55 (d, $J = 6.7$ Hz, 3H).

Hydrolysis of (*P*)-15a to (*P*)-1-carboxyphenyl(2-trifluoromethyl)benzimidazole (*P*-1)

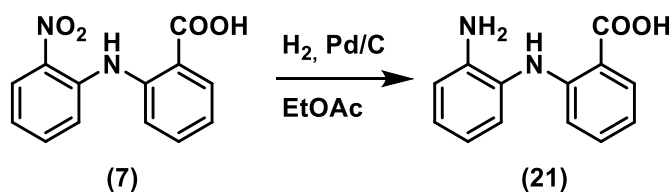


(*S,P*)-4-phenyl-2-(2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)phenyl)-4,5-dihydrooxazole (*P*)-**15a** (807 mg, 2 mmol, 1 eq.) was dissolved in MeOH (20 mL) and 10% (v/v) HCl (7.2 mL) was added. The solution was stirred at room temperature for 90 minutes when HPLC analysis showed complete ring opening. After 90 minutes, NaOH (1.6g, 40 mmol, 20 eq.) was added as a 10% aq. solution (16 mL). The reaction was stirred for another 3 hours until HPLC analysis showed a complete conversion. The solution was then diluted with water (15 mL), methanol was evaporated using RVO and a resulting solution was extracted with DCM (3x20 mL). The alkaline aq. phase was then added dropwise to ice cold 10% (v/v) HCl (30 mL) with rapid stirring. A white precipitate was collected by filtration and dried on air to give 393 mg of a white solid (64%). The compound was identical as racemic acid **rac-1** (with regards to spectroscopic properties NMR, MS, MP). $[\alpha]_D^{24} = -46.02^\circ$ (c= 1, MeOH). Enantiomeric purity was determined by chiral SFC: isocratic elution with 90% CO₂, 10% MeOH 0.1% TFA, column CHIRALPAK 1A3.

Hydrolysis of (*M*)-15a to (*M*)-1-carboxyphenyl(2-trifluoromethyl)benzimidazole (*M*-1)

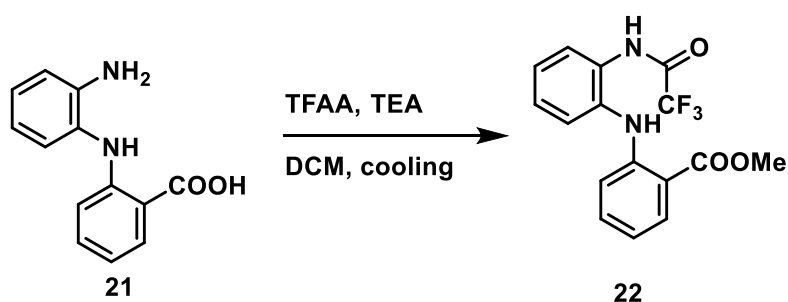
Following the above-described procedure, starting with 676 mg of oxazoline (*M*)-**15**. 324 mg of white solid (64%) $[\alpha]_D^{24} = +45.54^\circ$ (c= 1, MeOH).

2-((2-Aminophenyl)amino)benzoic acid (**21**)



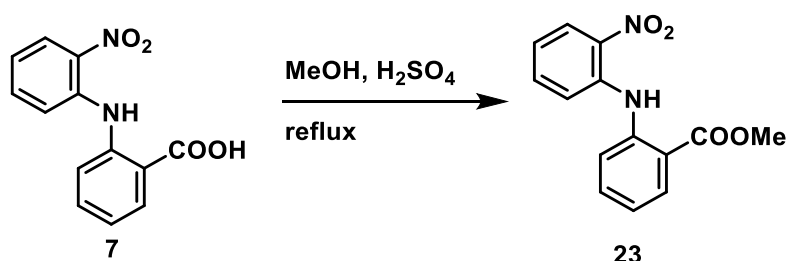
A two liter three-necked flask was charged with 2-((2-nitrophenyl)amino)benzoic acid **7** (16.8 g, 65 mmol, 1 eq.) and 10% Pd/C (1.3 g, 0.01 eq.). A solid mixture was suspended in ethyl acetate (1 L). The flask was fitted with a large stir bar, rubber balloon, valve and rubber septa, and flushed with nitrogen and vacuum multiple times to remove air. To an evacuated apparatus, a hydrogen gas was introduced and the reaction mixture was rapidly stirred at room temperature (500 rpm). The reaction was monitored by TLC (hexane: ethyl acetate 1:1, UV and ninhydrin detection) (a sample can be taken via syringe through rubber septum). After two hours, the mixture was filtered through pad of celite. Celite was washed twice with ethyl acetate and a filtrate was evaporated. Yield 14.3 g (96%), a yellow to brown solid. ¹H NMR (400 MHz, DMSO-D₆) δ 9.02 (s, 1H), 7.86 (dd, J = 7.9, 1.4 Hz, 1H), 7.28 (ddd, J = 8.5, 7.2, 1.5 Hz, 1H), 7.03 (dd, J = 7.7, 1.1 Hz, 1H), 6.99 – 6.93 (m, 1H), 6.80 (dd, J = 8.0, 1.2 Hz, 1H), 6.66 (td, J = 7.6, 0.9 Hz, 1H), 6.62 – 6.56 (m, 2H). ¹³C NMR {¹H} (101 MHz, DMSO-D₆) δ 170.60, 149.73, 144.68, 134.57, 132.07, 126.82, 126.65, 125.26, 117.08, 116.38, 115.94, 113.75, 111.79, HRMS ESI[M+H]⁺ calculated for C₁₃H₁₀O₂N₂+H: 229.0972, found: 229.0973, Mp: 195-200°C.

methyl 2-((2-(2,2,2-trifluoroacetamido)phenyl)amino)benzoate (22)



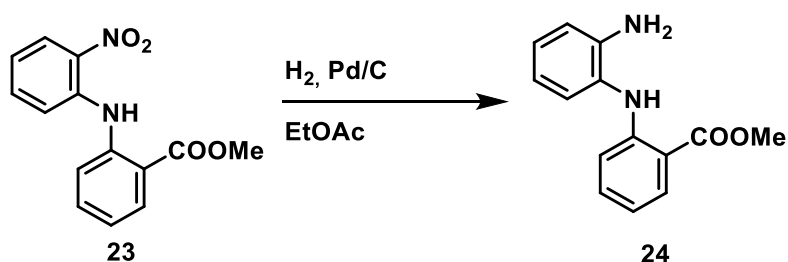
21 (228 mg, 1 mmol, 1 eq) was dissolved in DCM (6 mL) and trimethylamine (157 μ L, 1.1 mmol, 1.1 eq) was added. This solution was cooled in ice bath and TFAA (200 μ L, 1.1 mmol, 1.1 eq) in DCM (4 mL) was added dropwise. Reaction mixture was stirred for 40 minutes. After 40 minutes, water (5 mL) was added, and the precipitate was filtered and dried. Isolated 120 mg (37 %) $^1\text{H NMR}$ (400 MHz, DMSO- d_6) δ 11.25 – 10.97 (m, 1H), 9.80 – 9.51 (m, 1H), 7.89 (d, $J = 7.4$ Hz, 1H), 7.55 – 7.51 (m, 1H), 7.44 – 7.32 (m, 3H), 7.18 (q, $J = 7.7$ Hz, 1H), 7.10 – 7.02 (m, 1H), 6.78 (t, $J = 7.5$ Hz, 1H).

methyl 2-((2-nitrophenyl)amino)benzoate (23)



7 (10 g, 38.7 mmol) was dissolved in MeOH (200 mL) and conc. H₂SO₄ (3 mL) was added. The mixture was refluxed for 24 hrs. During this time, orange precipitate started to appear. After 24 hours, the reaction was cooled down to room temperature and the precipitate was filtered, washed with MeOH and dried. Yield 10.5 g (99%) of orange solid. $^1\text{H NMR}$ (400MHz, DMSO- d_6) $\delta = 10.90$ (s, 1 H), 8.15 (td, $J = 1.1, 8.3$ Hz, 1 H), 8.00 - 7.95 (m, 1 H), 7.63 - 7.63 (m, 0 H), 7.66 - 7.52 (m, 4 H), 7.16 - 7.05 (m, 2 H), 3.89 - 3.88 (m, 3 H) $^{13}\text{C NMR}$ { ^1H } (101MHz, DMSO- d_6) $\delta = 167.0, 141.8, 138.1, 137.0, 135.5, 134.0, 131.4, 126.3, 122.0, 120.7, 119.2, 119.0, 117.7, 52.3$ HRMS ESI[M+H]⁺ calculated for C₁₄H₁₃O₄N₂: 273.0870, found: 273.0872

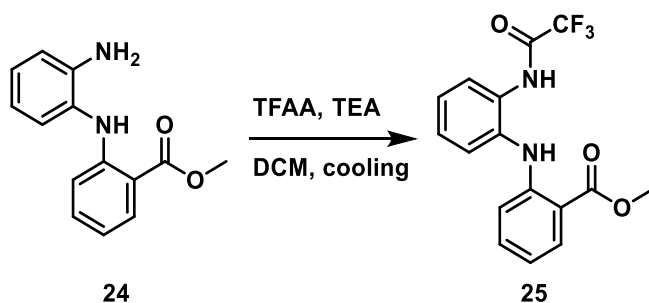
methyl 2-((2-aminophenyl)amino)benzoate (24)



Three-necked 2L flask fitted with stirrer, rubber septa and valve was charged with 4400 mg of 10% Pd/C (4.135 mmol, 0.05 eq). **23** (22.5 g, 82.7 mmol, 1 eq) was added followed by EtOAc (830 mL). The last open neck was fitted with rubber balloon and the whole apparatus was purged with argon / vacuum cycle three times. After the evacuation of the flask, hydrogen gas was introduced, and the suspension was rapidly stirred at room temperature for 18 hours (Hydrogen gas was reintroduced if necessary). After 18 hours, the flask was opened to air, the suspension was filtered through pad of silica and the filtrate was evaporated yielding 18.1 g (90%) of gray solid. $^1\text{H NMR}$ (400 MHz, CDCl₃) δ 8.76 (s, 1H), 7.86 (dd, $J = 8.0, 1.6$ Hz, 1H), 7.31 (ddd, $J = 8.6, 7.1, 1.7$ Hz, 1H), 7.03 (dd, $J = 7.8, 1.4$ Hz, 1H), 6.98 (td, $J = 7.7, 1.5$ Hz, 1H), 6.80 (dd, $J = 8.0, 1.4$ Hz, 1H), 6.68 (ddd, $J = 8.1, 7.1, 1.1$ Hz, 1H), 4.89 (s,

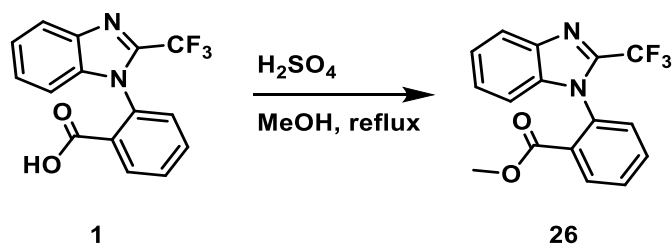
2H), 3.85 (s, 3H). $^{13}\text{C NMR}$ $\{^1\text{H}\}$ (101 MHz, CDCl_3) δ 168.2, 149.0, 144.3, 134.4, 131.0, 126.5, 126.4, 124.5, 116.6, 116.0, 115.5, 113.4, 110.5, 51.8. **HRMS** ESI $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{14}\text{H}_{15}\text{O}_2\text{N}_2$: 243.1128, found: 243.1129

methyl 2-((2-(2,2,2-trifluoroacetamido)phenyl)amino)benzoate (25)



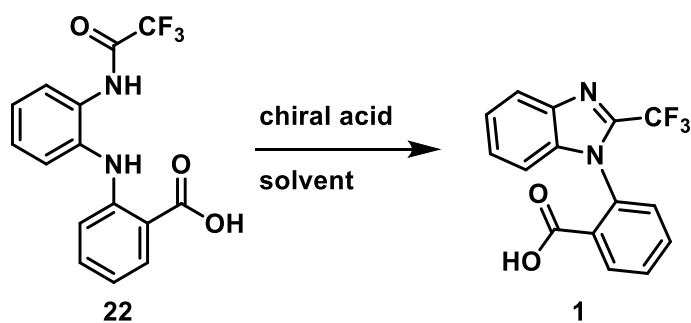
24 (242 mg, 1 mmol, 1 eq) was dissolved in DCM (10 mL), trimethylamine (155 μL , 1.1 mmol, 1.1 eq) was added and the reaction was cooled in ice bath. Trifluoroacetic acid anhydride (200 μL , 1.1 mmol, 1.1 eq) was added dropwise and the reaction mixture was stirred for 1 hour in ice bath. After 1 hours, water (10 mL) was added, and the organic layer was separated. The organic layer was further washed with 10% HCl (1x 10 mL), 10% K_2CO_3 (1x 10 mL), dried with MgSO_4 and evaporated to yield 282 mg of product (67%) $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 9.11 (s, 1H), 8.50 (s, 1H), 8.33 (dd, $J = 8.1, 1.4$ Hz, 1H), 8.02 (dd, $J = 8.0, 1.7$ Hz, 1H), 7.43 – 7.21 (m, 5H), 6.90 – 6.77 (m, 1H), 6.54 (dd, $J = 8.4, 1.1$ Hz, 1H), 3.95 (s, 3H). $^{13}\text{C NMR}$ $\{^1\text{H}\}$ (101 MHz, CDCl_3) δ 169.2, 148.9, 134.8, 132.7, 131.8, 131.2, 127.5, 127.4, 126.9, 121.4, 118.6, 114.4, 114.3, 112.7, 52.2.

methyl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (26)



1 (150 mg, 0.5 mmol, 1 eq) was dissolved in MeOH (20 mL) and conc. H_2SO_4 (0.5 mL) was added, and the reaction was refluxed for 16 hours. After 16 hours, the solvent was evaporated and the residue was diluted with water (10 mL) and basified with 10% aq. K_2CO_3 (25 mL) followed by extraction with EtOAc (3x 20 mL). The combined organic extracts were washed with 10% K_2CO_3 (25 mL), brine, dried with MgSO_4 and evaporated to yield 130 mg of yellow oil (80%). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.22 (dd, $J = 7.7, 1.8$ Hz, 1H), 7.96 – 7.92 (m, 1H), 7.77 (td, $J = 7.6, 1.7$ Hz, 1H), 7.70 (td, $J = 7.7, 1.4$ Hz, 1H), 7.50 (dd, $J = 7.7, 1.1$ Hz, 1H), 7.42 – 7.37 (m, 1H), 7.35 (td, $J = 7.7, 7.2, 1.4$ Hz, 1H), 6.99 – 6.96 (m, 1H), 3.46 (s, 3H). $^{13}\text{C NMR}$ $\{^1\text{H}\}$ (101 MHz, CDCl_3) δ 164.5, 141.09 (q, $J = 38.3$ Hz), 140.7, 137.6, 134.1, 133.6, 132.3, 130.5, 130.0, 128.9, 125.9, 123.9, 121.4, 118.92 (q, $J = 271.8$ Hz), 110.7, 52.4

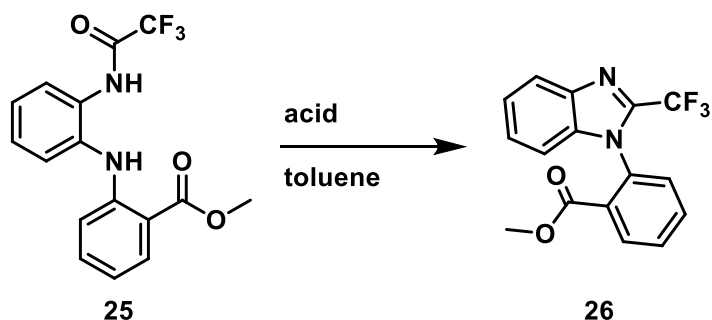
Atroposelective cyclization to (1)



22 (68 mg, 0.2 mmol, 1 eq) was dissolved in toluene (2 mL) and acid (10 mol%) was added. The mixture was heated to desired temperature for 24 hours. After 24 hours, sample was taken and analyzed by chiral SFC. In the case of the dibenzoyl-L-tartaric acid (entry 2) precipitate was formed which was removed by filtration and analyzed separately.

Entry	Acid	Solvent	Er
1	10-CSA	THF (65°C)	25 / 75
2	Dibenzoyl-L-tartaric acid	THF (65°C)	26 / 74 (solution) 50 / 50 (precipitate)
3	Dianisoyl-L-tartaric acid	THF (65°C)	26 / 74
4	Ditoluoyl-L-tartaric acid	THF (65°C)	26 / 74
5	L-proline	THF (65°C)	40 / 60
6	R-Mandelic acid	THF (65°C)	28 / 72
7	S-TRIP	THF (65°C)	Nd
8	10-CSA	Toluene (80°C)	Nd
9	Dibenzoyl-L-tartaric acid	Toluene (80°C)	Nd
10	Dianisoyl-L-tartaric acid	Toluene (80°C)	Nd
11	Ditoluoyl-L-tartaric acid	Toluene (80°C)	Nd
12	L-proline	Toluene (80°C)	Nd
13	R-Mandelic acid	Toluene (80°C)	Nd
14	TBBA	Toluene (80°C)	Nd
15	S-TRIP	Toluene (80°C)	Nd

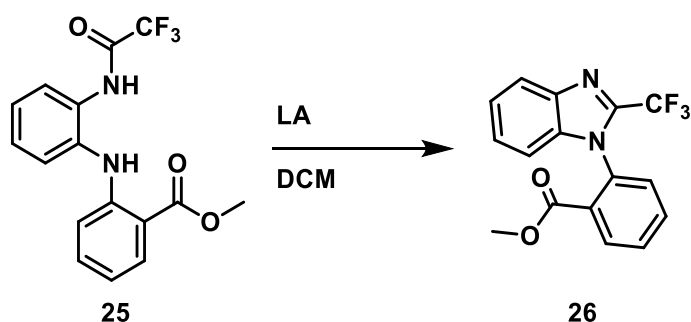
Atroposelective cyclization to (26)



25 (68 mg, 0.2 mmol, 1 eq) was dissolved in toluene (2 mL) and acid (10 mol%) was added. The mixture was heated to desired temperature for 24 hours. After 24 hours, sample was taken and analyzed by chiral SFC. Unfortunately, no product was detected.

Entry	Acid	Solvent + Temperature	Results
1	10-CSA	Toluene (80°C)	Nd
2	Dibenzoyl-L-tartaric acid	Toluene (80°C)	Nd
3	Dianisoyl-L-tartaric acid	Toluene (80°C)	Nd
4	Ditoluoyl-L-tartaric acid	Toluene (80°C)	Nd
5	L-proline	Toluene (80°C)	Nd
6	R-Mandelic acid	Toluene (80°C)	Nd
7	TBBA	Toluene (80°C)	Nd
8	S-TRIP	Toluene (80°C)	Nd
9	10-CSA	Toluene (120°C)	Nd
10	Dibenzoyl-L-tartaric acid	Toluene (120°C)	Nd
11	S-TRIP	Toluene (120°C)	Nd

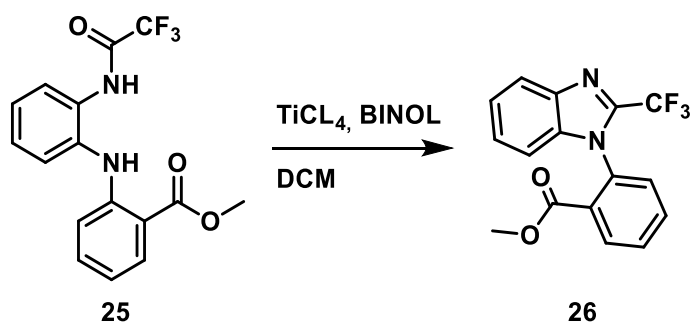
Lewis acid catalyzed cyclization to (26)



25 (85 mg, 0.25 mmol, 1 eq) was dissolved in dry DCM (2.5 mL), 4A molecular sieves were added and the mixture was cooled in ice bath. After the cooling, Lewis acid (0.5 mmol, 2 eq) was added. Reaction was stirred for 5 hours. After 5 hours, water (2 mL) was added and the mixture was filtered through celite. The organic layer was separated, dried with MgSO₄ and evaporated. The residue was analyzed by HPLC.

Entry	Lewis acid	Solvent	Results
1	SnCl ₄ , 2 eq.	DCM	Complex mixture
2	TiCl ₄ , 2 eq. (1M solution)	DCM	79%
3	Ti(OiPr) ₄ , 2 eq.	DCM	Complex mixture, low conversion
4	TiCl ₄ 0.2 eq	DCM	Traces of product
5	TiCl ₄ 0.5 eq	DCM	Traces of product
6	TiCl ₄ 1 eq	DCM	65 % isolated

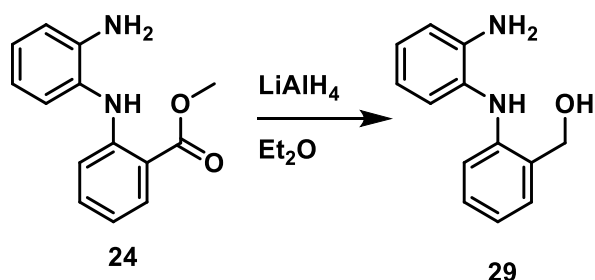
TiCl₄ catalyzed cyclization to (26)



(*R*)-BINOL (81 mg) was dissolved in dry DCM (2 mL) and molecular sieves were added. TiCl₄ (1M in DCM, 300 μ L, 1 eq) was added and the solution immediately turned red. This solution was stirred at room temperature for 1 hours. **25** was dissolved in dry DCM (1 mL) and to this solution the TiCl₄-BINOL solution was added (670 μ L or 1300 μ L). The reaction was stirred for 24 hours and after 24 hours was analyzed by HPLC. Due to low conversion no isolation was attempted.

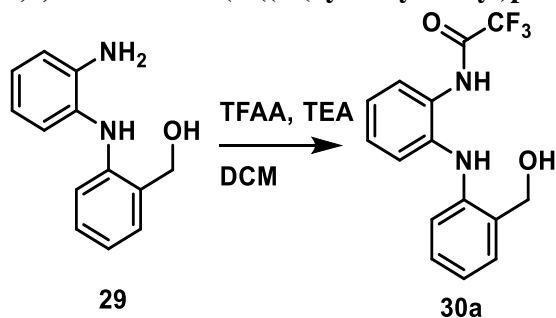
Entry	Eq. TiCl ₄	Solvent	Result
1	1 + 1eq. (<i>R</i>)-BINOL	DCM	10% conversion
2	2 + 2eq. (<i>R</i>)-BINOL	DCM	20% conversion, 50:50 er.

(2-((2-aminophenyl)amino)phenyl)methanol (**29**)



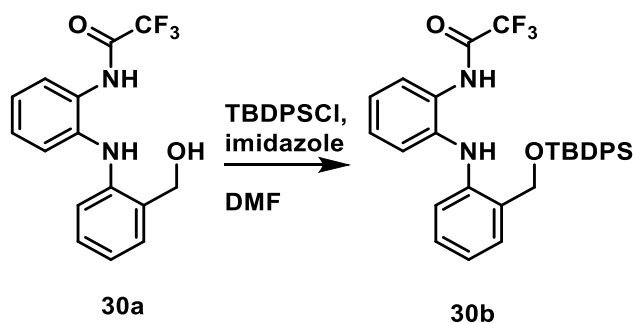
24 (968 mg, 4 mmol, 1eq) was added over 20 minutes as a solid into the suspension of LiAlH₄ (608 mg, 16 mmol, 4 eq) in dry diethyl ether (72 mL). This suspension was stirred at room temperature for 30 minutes. After 30 minutes, the reaction was cooled in ice bath and water (1.3 mL) was added. The mixture was stirred in ice bath for 30 minutes forming brown suspension. After 30 minutes, 15% aq. NaOH (610 μ L) and water (1.2 mL) were added and the reaction was stirred for 10 minutes. After 10 minutes, celite was added and the solids were removed by filtration. The filtrate was evaporated and purified by column chromatography (Hexane: EtOAc 2:1) to yield 500 mg of oil which solidified by standing on air (60%). ¹H NMR (400 MHz, CDCl₃) δ 7.19 – 7.12 (m, 2H), 7.11 – 7.08 (m, 1H), 7.02 (ddd, *J* = 7.9, 7.4, 1.5 Hz, 1H), 6.82 – 6.76 (m, 3H), 6.70 (d, *J* = 7.7 Hz, 1H), 6.39 (s, 1H), 4.75 (s, 2H), 3.24 (s, 2H). ¹³C NMR {¹H} (101 MHz, CDCl₃) δ 144.9, 141.2, 129.5, 129.5, 128.7, 125.9, 125.5, 125.0, 119.5, 118.9, 116.5, 114.5, 64.7.

2,2,2-trifluoro-*N*-(2-((2-(hydroxymethyl)phenyl)amino)phenyl)acetamide (30a)



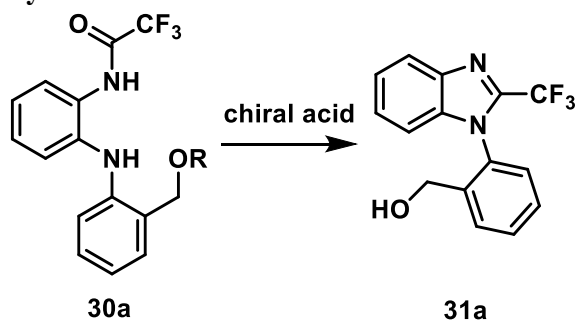
29 (50 mg, 0.23 mmol, 1 eq) was dissolved in dry DCM (2.5 mL). Triethylamine (49 μ L, 0.35 mmol, 1.5 eq) was added and the mixture was cooled in ice bath. TFAA (49 μ L, 0.35 mmol, 1.5 eq) dissolved in dry DCM (0.5 mL) was slowly added and the reaction was stirred at room temperature for 2 hours. After 2 hours, reaction was diluted with DCM (5 mL) and the solution was washed with 10% K_2CO_3 (3x 5 mL) and 10% HCl (1x 5 mL), dried with $MgSO_4$ and evaporated. The residue was purified by column chromatography (hexane: EtOAc 4:1) to yield 40 mg (56%) of product as oil. 1H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 8.11 – 8.06 (m, 1H), 7.22 (dt, J = 6.3, 3.2 Hz, 3H), 7.19 – 7.12 (m, 3H), 6.86 (td, J = 7.4, 1.0 Hz, 2H), 6.64 – 6.59 (m, 1H), 4.80 (s, 2H).

***N*-(2-(((tert-butyl)diphenylsilyloxy)methyl)phenyl)amino)phenyl)-2,2,2-trifluoroacetamide (30b)**



30a (184 mg, 0.6 mmol, 1eq) was dissolved in dry DMF (6 mL). Imidazole (98 mg, 1.44 mmol, 2.4 eq) was added followed by TBDPSCI (182 μ L, 0.71 mmol, 1.2 eq). Reaction was stirred at room temperature for 4 hours. After 4 hours, reaction was diluted with water (20 mL) and extracted into ethyl acetate (3x 20 mL). Combined organic extracts were washed with 10% HCl (2x 20 mL), 10% aq. K_2CO_3 (2x 20 mL) and brine. Organic extracts were dried with $MgSO_4$ and evaporated. The residue was purified by column chromatography (Hex: EtOAc 350:15) to yield 157 mg of the product (50%). 1H NMR (400 MHz, $CDCl_3$) δ 10.57 (s, 1H), 7.63 (d, J = 6.8 Hz, 4H), 7.53 (d, J = 7.5 Hz, 1H), 7.43 (dq, J = 14.3, 7.1 Hz, 6H), 7.25 (d, J = 7.8 Hz, 1H), 7.17 (t, J = 7.5 Hz, 1H), 7.12 (t, J = 7.7 Hz, 1H), 7.06 (t, J = 7.4 Hz, 1H), 6.91 (t, J = 7.6 Hz, 1H), 6.82 (q, J = 8.1 Hz, 3H), 4.81 (s, 2H), 1.02 (s, 9H). ^{13}C NMR { 1H } (101 MHz, $CDCl_3$) δ 155.17 (q, J = 36.4 Hz), 139.9, 139.5, 135.0, 132.9, 132.0, 129.9, 128.0, 127.9, 127.5, 127.2, 126.5, 124.6, 122.1, 120.6, 119.9, 119.3, 115.88 (d, J = 288.9 Hz), 62.1, 26.7, 18.9.

Cyclization to 31a

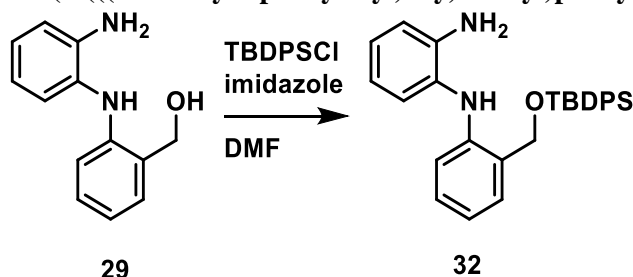


30a (135 mg, 0.45 mmol, 1eq) was dissolved in toluene (6 mL) and this solution was separated into 6 reaction vials. To each vial, catalytical amount of the acid was added and the reaction was heated to 65°C for 24 hours. After 24 hours, the reaction was cooled to room temperature, washed with K₂CO₃ (1x 1.5 mL), brine, dried with MgSO₄ and evaporated. ¹H NMR (400 MHz, CDCl₃) δ 7.95 (d, *J* = 8.1 Hz, 1H), 7.78 (d, *J* = 7.3 Hz, 1H), 7.67 – 7.62 (m, 2H), 7.53 – 7.48 (m, 2H), 7.44 – 7.35 (m, 6H), 7.33 (d, *J* = 7.9 Hz, 2H), 7.02 (d, *J* = 7.4 Hz, 2H), 4.33 (q, *J* = 13.7 Hz, 2H).

Entry	Acid	Solvent + temperature	Results
1	Dibenzoyl-L-tartaric acid	Toluene 65°C	No reaction
2	Dianisoyl-L-tartaric acid	Toluene 65°C	No reaction
3	Ditoluoyl-L-tartaric acid	Toluene 65°C	No reaction
4	(<i>S</i>)-TRIP	Toluene 65°C	Er. 73/27
5	10-CSA	Toluene 65°C	Er. 32/68*
6	(<i>S</i>)-TRIP	Toluene 85°C	decomposition

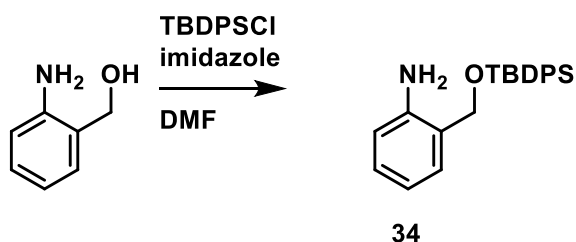
* Overlapping peaks allowed only approximate integration.

N1-(2-(((tert-butyldiphenylsilyloxy)methyl)phenyl)benzene-1,2-diamine (32)



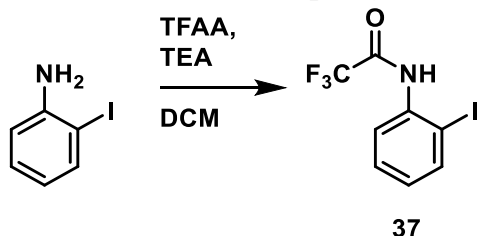
29 (241 mg, 1 mmol, 1eq) was dissolved in dry DMF (5 mL) and imidazole (163 mg, 2.4 mmol, 2.4 eq) was added followed by TBDPSCI (308 μL, 1.2 mmol, 1.2 eq). Reaction was stirred at room temperature for 18 hours. Afterwards, water (20 mL) was added, and the solution was extracted with EtOAc (3x 20 mL). Organic extracts were combined and washed with 10% aq. HCl (2x 20 mL) and 10% aq. K₂CO₃ (2x 20 mL), brine and dried with MgSO₄ and evaporated. The residue was purified by column chromatography (Hexane: EtOAc 20:1) to isolate 350 mg of product (75%) ¹H NMR (400 MHz, CDCl₃) δ 7.73 – 7.63 (m, 5H), 7.51 – 7.35 (m, 8H), 7.09 – 7.03 (m, 1H), 6.81 (ddd, *J* = 17.9, 8.0, 1.1 Hz, 3H), 6.71 (dd, *J* = 7.9, 1.3 Hz, 1H), 6.55 – 6.45 (m, 2H), 6.42 (s, 1H), 4.86 (s, 2H), 4.62 (s, 2H), 1.05 (s, 9H). ¹³C NMR {¹H} (101 MHz, CDCl₃) δ 142.6, 142.4, 136.4, 135.0, 134.5, 133.0, 129.9, 129.2, 127.9, 127.8, 127.6, 127.5, 126.4, 124.3, 123.7, 118.7, 116.7, 115.1, 114.9, 62.8, 26.7, 18.9.

2-(((tert-butyl)phenylsilyloxy)methyl)aniline (**34**)



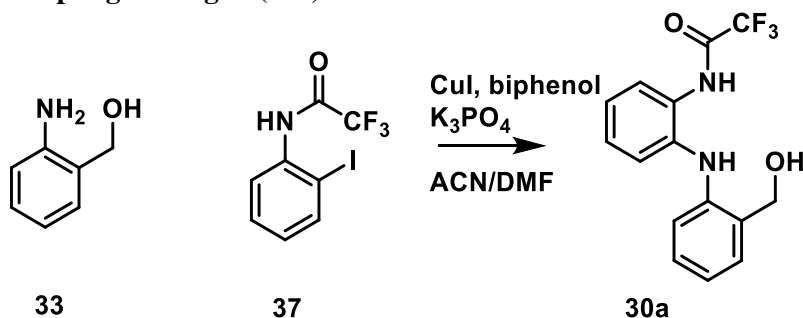
2-hydroxymethylaniline (123 mg, 1 mmol, 1 eq) was dissolved in dry DMF. Imidazole (163 mg, 2.5 mmol, 2.4 eq) was added followed by TBDPSCI (308 μ L, 1.2 mmol, 1.2 eq). Reaction was stirred at room temperature for 18 hours. Afterwards, water (20 mL) was added, and the solution was extracted with EtOAc (3x 20 mL). Organic extracts were combined and washed with sat. aq. NH_4Cl (2x 20 mL) and brine and dried with MgSO_4 and evaporated to yield 270 mg of oil (75%) $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.65 (d, $J = 7.1$ Hz, 4H), 7.52 – 7.35 (m, 7H), 7.14 (d, $J = 7.5$ Hz, 1H), 6.98 (t, $J = 7.6$ Hz, 1H), 6.65 (d, $J = 7.8$ Hz, 1H), 6.57 (t, $J = 7.3$ Hz, 1H), 4.87 (s, 2H), 4.66 (s, 2H), 1.03 (s, 9H). $^{13}\text{C NMR}$ { ^1H } (101 MHz, CDCl_3) δ 145.6, 135.0, 134.5, 133.0, 129.9, 127.9, 127.6, 127.5, 126.3, 123.8, 116.0, 114.7, 63.2, 26.7, 18.9.

2,2,2-trifluoro-*N*-(2-iodophenyl)acetamide (**37**)



2-iodoaniline (219 mg, 1 mmol, 1 eq) and triethylamine (193 μ L, 1.5 mmol, 1.5 eq) were dissolved in dry DCM (4 mL) and the solution was cooled in ice bath. TFAA (168 μ L, 1.2 mmol, 1.2 eq) was added dropwise and the reaction was stirred for 16 hours at room temperature. After 16 hours, TLC (hexane: EtOAc 5:1) revealed unreacted starting material. TEA (193 μ L, 1.5 mmol, 1.5 eq) and TFAA (140 μ L, 1 mmol, 1 eq) were subsequently added and the reaction was stirred at room temperature for 4 hours. After 4 hours, the reaction was diluted with DCM (10 mL) and washed with 10% aq. K_2CO_3 (3x 15 mL) 10% HCl (3x 15 mL). The organic layer was dried with MgSO_4 and evaporated to yield 155 mg (50%) $^1\text{H NMR}$ (400 MHz, $\text{DMSO-}d_6$) δ 11.24 (s, 1H), 7.96 (dd, $J = 7.9, 1.4$ Hz, 1H), 7.48 (td, $J = 7.6, 1.5$ Hz, 1H), 7.38 (dd, $J = 7.9, 1.7$ Hz, 1H), 7.15 (td, $J = 7.6, 1.7$ Hz, 1H).

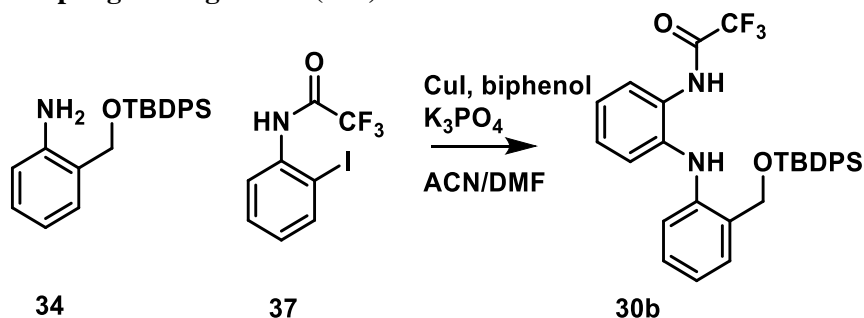
Coupling leading to (**30a**)



5 mL flame dried Schlenk tube with Teflon coated stir bar was charged with **33** (70 mg, 0.22 mmol, 1eq), biphenol (3.72 mg, 0.01 mmol, 0.1 eq) and K_3PO_4 (102 mg, 0.22 mmol, 2.2 eq). The Schlenk tube was evacuated and backfilled with argon three times. Separate flask was charged with **37** (54 mg, 0.44 mmol, 2 eq) and evacuated and backfilled with argon three times. Dry acetonitrile (dried over activated mol. Sieves for 3 days, 500 μ L) and dry DMF (1 mL) were added, and the subsequent cloudy solution was added to the Schlenk flask containing compound **33**. Reaction was heated to 65 $^\circ\text{C}$ for 18 hours.

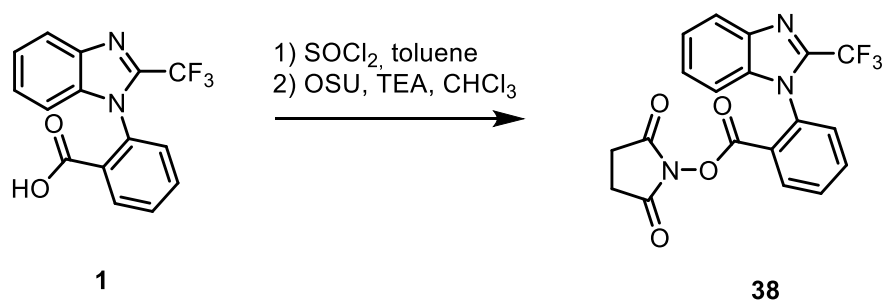
After 18 hours, reaction was cooled to room temperature, diluted with EtOAc (10 mL) and washed with sat. aq. NaHCO₃ (3x 10 mL), 10% HCl (3x 10 mL) and brine. The organic layer was evaporated and purified by column chromatography (Hexane: EtOAc 5:1) to yield 15 mg of the product (25%).

Coupling leading to and (30b)



5 mL flame dried Schlenk tube with Teflon coated stir bar was charged with **34** (31mg, 0.1 mmol, 1eq), biphenol (1.86 mg, 0.01 mmol, 0.1 eq) and K₃PO₄ (47 mg, 0.22 mmol, 2.2 eq). The Schlenk tube was evacuated and backfilled with argon three times. Separate flask was charged with **37** (72mg, 0.2 mmol, 2 eq) and evacuated and backfilled with argon three times. Dry acetonitrile (dried over activated mol. Sieves for 3 days, 500 μL) and dry DMF (1 mL) were added, and the subsequent cloudy solution was added to the Schlenk flask containing compound **34**. Reaction was heated to 65°C for 18 hours. Neither TLC or HPLC analysis showed any conversion of starting material.

2,5-dioxopyrrolidin-1-yl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (38)



1 (1 g, 3.26 mmol, 1 eq) was dissolved in toluene (45 mL) and SOCl₂ (1.22 mL, 16.8 mmol, 5 eq) was added. This mixture was refluxed until the acid was not fully dissolved. Afterwards, the reaction mixture was evaporated, dissolved in CHCl₃ and evaporated again. The residue was dissolved in dry DCM (10 mL) and was added slowly into the suspension of N-hydroxysuccinimide (375 mg, 3.58 mmol, 1.1 eq) and trimethylamine (450 μL, 3.58 mmol, 1.1 eq) in dry DCM (10 mL). After the addition was complete, the reaction was stirred at room temperature for 18 hours. After 18 hours, the reaction was extracted with water (3x 20 mL), dried with MgSO₄ and evaporated to yield 1.26 g (95%). ¹H NMR (400 MHz, CDCl₃) δ 8.40 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.91 (dddd, *J* = 7.8, 6.0, 3.1, 1.4 Hz, 2H), 7.79 (td, *J* = 7.8, 1.3 Hz, 1H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.42 – 7.35 (m, 2H), 7.03 – 6.98 (m, 1H), 2.69 (s, 4H). ¹³C NMR (101 MHz, CDCl₃) δ 168.5, 159.0, 140.8, 140.8 (q, *J* = 38.6 Hz) 137.3, 135.7, 135.3, 132.9, 131.0, 130.9, 126.3, 124.2, 121.5, 118.80 (q, *J* = 272.2 Hz), 110.8, 25.5. ¹⁹F NMR (376 MHz, CDCl₃) δ -61.3.

General procedure for TBBA-amide formation

(*P*)-(*R*)-*N*-(1-Phenylethyl)-2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzamide (*M*)-**39**

(*P*)-1-Carboxyphenyl(2-trifluoromethyl)benzimidazole (*P*)-**1** (40 mg, 0.13 mmol, 1 eq) was dissolved in DMF (0.8 mL). EDCI (51 mg, 0.26 mmol, 2 eq) and then HOBt (40 mg, 0.26 mmol, 2 eq) were subsequently added into the solution. Afterwards, (*R*)-(+)-1-Phenylethylamine (18.2 μL, 0.143 mmol, 1.1 eq) was added into the mixture and the reaction was stirred at room temperature (23-25°C) until a complete conversion of the starting material was detected by HPLC analysis (90-120 min). After

completion, the reaction was diluted with 4 ml of EtOAc forming a cloudy white solution, which was extracted with 10% HCl (2x 4ml), sat. NaHCO₃ (2x 4 ml), and brine (4 ml). The organic layer was dried over Na₂SO₄ and evaporated to give 24 mg of a white solid (47%). ¹H NMR (400 MHz, CDCl₃) δ 7.83 – 7.78 (m, 1H), 7.67 – 7.60 (m, 2H), 7.39 (ddd, *J* = 15.5, 10.2, 6.3 Hz, 3H), 7.26 – 7.19 (m, 3H), 7.09 (d, *J* = 7.7 Hz, 1H), 7.00 – 6.95 (m, 2H), 5.59 (d, *J* = 7.4 Hz, 1H), 4.84 (p, *J* = 7.0 Hz, 1H), 0.92 (d, *J* = 6.8 Hz, 3H). ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 164.4, 142.1, 140.6, 137.5, 135.3, 131.7, 131.5, 130.8, 129.9, 129.5, 128.8, 127.7, 126.5, 126.05, 124.5, 121.7, 119.0 (q, *J* = 272.0 Hz), 49.4, 20.7 ¹⁹F NMR (376 MHz, CDCl₃) δ -61.21 ¹⁵N NMR (50.664 MHz, CDCl₃): δ -128.8, -226.4, -247.3 (¹*J*=89.5 Hz) HRMS (ESI) *m/z*: [M+H]⁺ calculated for C₂₃H₁₉ON₃F₃: 410.1475, found: 410.1472, [α]_D²² = -21.89° (c= 0.50, MeOH).

(M)-(R)-N-(1-Phenylethyl)-2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzamide (M)-39, From 40 mg of (M)-1 and R-(+)-1-Phenylethylamine, 43 mg of a white solid (81%). ¹H NMR (400 MHz, CDCl₃) δ 7.96 (d, *J* = 8.1 Hz, 1H), 7.91 – 7.86 (m, 1H), 7.70 – 7.62 (m, 2H), 7.47 – 7.34 (m, 3H), 7.19 – 7.10 (m, 3H), 7.06 (d, *J* = 8.2 Hz, 1H), 6.73 – 6.69 (m, 2H), 5.48 (d, *J* = 7.0 Hz, 1H), 4.86 (p, *J* = 7.0 Hz, 1H), 1.12 (d, *J* = 6.8 Hz, 3H). ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 164.3, 141.9, 140.7, 137.5, 135.3, 131.8, 131.3, 130.9, 130.2, 129.5, 128.7, 127.55, 126.5, 125.8, 124.5, 122.0, 118.8 (q, *J* = 272.3 Hz), 111.1, 49.5, 21.1 ¹⁹F NMR (376 MHz, CDCl₃) δ -61.49 ¹⁵N NMR (50.664 MHz, CDCl₃): δ -129.5, -226.2, -247.4 (¹*J*=89.1 Hz) HRMS (ESI) *m/z*: [M+H]⁺ calculated for C₂₃H₁₉ON₃F₃: 410.1475, found: 410.1475, [α]_D²² = +159.59° (c= 0.73, MeOH).

(P)-(S)-N-(1-phenylethyl)-2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzamide (P)-40 From 40 mg of *I-P* and S-(-)-1-Phenylethylamine, 25 mg of white solid (47%). ¹H NMR (400 MHz, CDCl₃) δ 7.96 (d, *J* = 8.2 Hz, 1H), 7.90 – 7.85 (m, 1H), 7.68 – 7.62 (m, 2H), 7.41 (ddt, *J* = 20.8, 16.0, 4.0 Hz, 3H), 7.19 – 7.09 (m, 3H), 7.06 (d, *J* = 8.2 Hz, 1H), 6.71 (dd, *J* = 7.7, 1.8 Hz, 2H), 5.52 (d, *J* = 7.0 Hz, 1H), 4.85 (p, *J* = 7.0 Hz, 1H), 1.12 (d, *J* = 6.8 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 164.2 (s), 141.9 (s), 141.1 (s), 140.7 (s), 137.5 (s), 135.4 (s), 131.8 (s), 131.4 (s), 130.9 (s), 130.2 (s), 129.5 (s), 128.8 (s), 127.6 (s), 126.55 (s), 125.8 (s), 124.5 (s), 121.9 (s), 118.9 (q, *J* = 271.7 Hz), 111.1 (s), 49.5 (s), 21.1 (s). ¹⁹F NMR (376 MHz, CDCl₃) δ -61.49 (s). HRMS (ESI) [M+H]⁺ calculated for C₂₃H₁₈ON₃F₃+H: 410.1475, found: 410.1473, [α]_D²² = -157.10° (c= 0.92, MeOH).

(M)-(S)-N-(1-phenylethyl)-2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzamide (M)-40 From 40 mg of *I-M* and S-(-)-1-Phenylethylamine, 38 mg of white solid (70%) ¹H NMR (400 MHz, CDCl₃) δ 7.94 (dd, *J* = 7.0, 1.5 Hz, 1H), 7.85 – 7.80 (m, 1H), 7.68 – 7.63 (m, 2H), 7.45 – 7.36 (m, 3H), 7.26 – 7.20 (m, 3H), 7.10 (dd, *J* = 7.1, 1.5 Hz, 1H), 6.99 (dd, *J* = 7.5, 1.7 Hz, 2H), 5.58 (d, *J* = 7.4 Hz, 1H), 4.85 (p, *J* = 7.0 Hz, 1H), 0.93 (d, *J* = 6.8 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 164.5 (s), 142.05 (s), 140.5 (s), 137.5 (s), 135.3 (s), 131.7 (s), 131.5 (s), 130.8 (s), 129.8 (s), 129.5 (s), 128.8 (s), 127.7 (s), 126.5 (s), 126.0 (s), 124.5 (s), 121.65 (s), 119.0 (q, *J* = 272.5 Hz), 111.4 (s), 49.4 (s), 20.7 (s). ¹⁹F NMR (376 MHz, CDCl₃) δ -61.20 (s). HRMS (ESI) [M+H]⁺ calculated for C₂₃H₁₈ON₃F₃+H: 410.1475, found: 410.1478, [α]_D²² = +19.76° (c= 0.49, MeOH).

(P)-(R)-N-(1-(naphthalen-1-yl)ethyl)-2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzamide (P)-41 From 15 mg of (P)-1 and (R)-(+)-1-(1-Naphthyl)ethylamine, 17 mg of oil (74%). Purified by column chromatography (hexane: ethyl acetate 3:1, column dimensions 1x10 cm). ¹H NMR (500 MHz, CDCl₃) δ (ppm) = 7.90 (d, *J* = 7.5 Hz, 1H), 7.84 (d, *J* = 7.6 Hz, 1H), 7.75 (dd, *J* = 12.6, 5.3 Hz, 1H), 7.61 (pd, *J* = 7.4, 1.4 Hz, 1H), 7.51 – 7.43 (m, 1H), 7.38 (dt, *J* = 15.5, 7.3 Hz, 1H), 7.20 (d, *J* = 7.1 Hz, 1H), 7.11 (d, *J* = 7.6 Hz, 1H), 5.76 – 5.65 (m, 1H), 1.16 (d, *J* = 6.5 Hz, 1H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ (ppm) = 164.4, 140.6, 140.6 (app.d, *J* = 38.2 Hz), 137.7, 137.4, 135.6, 134.0, 131.7, 131.0, 130.8, 129.7, 128.9, 128.7, 126.8, 126.4, 126.0, 125.3, 124.4, 123.1, 122.6, 121.7, 119.0 (q, *J* =, 272.0 Hz), 111.5, 45.1, 19.9. ¹⁹F NMR (376 MHz, CDCl₃) δ (ppm) = -61.19. HRMS (ESI) *m/z*: [M+H]⁺ calculated for C₂₇H₂₁F₃N₃O: 460.1637 found: 460.1632, [α]_D²² -95.00° (c= 0.1 CHCl₃).

(M)-(R)-N-(1-(naphthalen-1-yl)ethyl)-2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzamide (M)-41

From 15 mg of (M)-2 and (R)-(+)-1-(1-Naphthyl)ethylamine, 15.5 mg of oil (68%). Purified by column chromatography (hexane: ethyl acetate 3:1, column dimensions 1x10 cm). ¹H NMR (500 MHz, CDCl₃) δ (ppm) = 7.88 (d, *J* = 8.2 Hz, 1H), 7.86 – 7.81 (m, 1H), 7.80 (d, *J* = 7.9 Hz, 1H), 7.71 (d, *J* = 8.2 Hz, 1H), 7.65 – 7.59 (m, 1H), 7.47 – 7.43 (m, 1H), 7.43 – 7.40 (m, 1H), 7.39 (dd, *J* = 5.9, 3.2 Hz, 1H), 7.37 – 7.33 (m, 1H), 7.27 (dd, *J* = 7.0, 1.0 Hz, 1H), 7.24 (d, *J* = 7.1 Hz, 1H), 6.98 (d, *J* = 8.2 Hz, 1H), 6.86 (d, *J* = 7.1 Hz, 1H), 5.72 (p, *J* = 6.8 Hz, 1H), 5.58 (d, *J* = 7.8 Hz, 1H), 1.26 (d, *J* = 6.7 Hz, 1H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ (ppm) = 164.1 (s), 141.1 (d, *J* = 38.6 Hz), 140.7, 137.5, 137.40, 135.3, 133.9, 131.8, 131.62, 130.9, 130.7, 130.0, 129.7, 128.8, 128.5, 126.7, 126.3, 126.0, 125.2, 124.4, 123.0, 122.2, 121.8, 119.0 (q), 110.9, 44.9, 20.3. ¹⁹F NMR (376 MHz, CDCl₃) δ (ppm) = -61.54. HRMS (ESI) m/z: [M+H]⁺ calculated for C₂₇H₂₁F₃N₃O: 460.1637 found: 460.1632, [α]_D²² +68.00° (c = 0.1 CHCl₃).

(P)-(S)-N-(3,3-dimethylbutan-2-yl)-2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzamide (P)-42

From 15 mg of (P)-1 and (S)-(+)-3,3-dimethyl-2-butylamine, 16.2 mg of oil (83%). Purified by column chromatography (hexane: ethyl acetate 4:1, column dimensions 1x10 cm). ¹H NMR (500 MHz, CDCl₃) δ(ppm) = 7.96 – 7.93 (m, 1H), 7.91 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.71 – 7.63 (m, 2H), 7.44 – 7.38 (m, 3H), 7.14 – 7.10 (m, 1H), 5.16 (d, *J* = 9.2 Hz, 1H), 3.69 (dq, *J* = 9.5, 6.8 Hz, 1H), 0.70 (d, *J* = 6.8 Hz, 3H), 0.48 (s, 9H). ¹³C{¹H} (126 MHz, CDCl₃) δ 164.7, 141.05 (q, *J* = 39.4 Hz), 140.85, 137.5, 135.9, 131.6, 131.1, 131.0, 130.4 129.6, 126.6, 124.7, 122.0, 118.94 (q, *J* = 272.1 Hz), 111.2, 53.6, 33.6, 25.7, 15.7. ¹⁹F NMR (376 MHz, CDCl₃) δ (ppm) = -61.42, HRMS (ESI) m/z: [M+H]⁺ calculated for C₂₁H₂₃F₃N₃O: 390.1793 found: 390.1788, [α]_D²² -80.00° (c = 0.1 CHCl₃).

(M)-(S)-N-(3,3-dimethylbutan-2-yl)-2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzamide (M)-42

Using method B, from 15 mg of (M)-1 and (S)-(+)-3,3-dimethyl-2-butylamine, 14,6 mg of oil (75 %). Purified by column chromatography (hexane: ethyl acetate 4:1, column dimensions 1x10 cm). ¹H NMR (500 MHz, CDCl₃) δ 7.94 – 7.90 (m, 1H), 7.88 – 7.85 (m, 1H), 7.67 (pd, *J* = 7.5, 1.7 Hz, 2H), 7.43 – 7.37 (m, 4H), 7.14 – 7.10 (m, 1H), 5.21 (d, *J* = 9.2 Hz, 1H), 3.65 (dq, *J* = 9.6, 6.8 Hz, 1H), 0.66 (s, 9H), 0.42 (d, *J* = 6.8 Hz, 3H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 164.9, 140.7, 140.5 (q, *J* = 38.4 Hz), 137.6, 135.9, 131.6, 131.2, 130.9, 130.00, 129.6, 126.6, 124.6, 121.7, 119.1 (q, *J* = 271.7 Hz), 111.6, 53.5, 33.8, 25.9, 15.1 ¹⁹F NMR (376 MHz, CDCl₃) δ (ppm) = -61.06. HRMS (ESI) m/z: [M+H]⁺ calculated for C₂₁H₂₃F₃N₃O: 390.1793 found: 390.1790, [α]_D²² = +155.56° (c = 0.09 CHCl₃).

(P)-(S)-N-(1-Cyklohexylethyl)-2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzamide (P)-43

From 20 mg (P)-1, (S)-1-cyklohexylethanamine (7,5 µl; 0,05 mmol; 0,8 eq.) purified by column chromatography (Hex/EtOAc 3:1) 17 mg of yellow oil (81%). ¹H NMR (500 MHz, CDCl₃) δ (ppm) = 7.96 – 7.93 (m, 1H), 7.91 – 7.89 (m, 1H), 7.70 – 7.61 (m, 2H), 7.44 – 7.37 (m, 3H), 7.13 – 7.11 (m, 1H), 5.16 (d, *J* = 8.2 Hz, 1H), 3.70 – 3.64 (m, 1H), 1.55 – 1.47 (m, 3H), 1.18 (dd, *J* = 12.8, 1.8 Hz, 1H), 1.10 (dd, *J* = 12.7, 1.9 Hz, 1H), 0.98 – 0.78 (m, 5H), 0.77 (d, *J* = 6.8 Hz, 3H), 0.52 – 0.43 (m, 1H), 0.37 (dt, *J* = 12.2, 7.8 Hz, 1H). ¹³C NMR (126 MHz, CDCl₃) δ (ppm) = 164.6, 140.9 (app. d, *J* = 38.0 Hz), 140.8, 137.5, 135.8, 131.6, 131.1, 130.9, 130.4, 129.5, 126.6, 124.6, 121.9, 119.0 (app. d, *J* = 272.2 Hz), 111.4, 50.0, 42.6, 28.6, 28.3, 26.2, 26.1, 26.1, 17.4. HRMS (ESI) m/z calc for C₂₃H₂₅F₃N₃O [M+H]⁺ 416.1950, found 416.1945. [α]_D²²: -120.00° (c = 0,13 MeOH).

(M)-(S)-N-(1-Cyklohexylethyl)-2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzamide (M)-43

From 20 mg (P)-1, (S)-1-cyklohexylethanamine (7,5 µl; 0,05 mmol; 0,8 eq.) purified by column chromatography (Hex/EtOAc 3:1) 15 mg of yellow oil (72%). ¹H NMR (500 MHz, CDCl₃) δ (ppm) = 7.94 – 7.92 (m, 1H), 7.86 – 7.84 (m, 1H), 7.69 – 7.62 (m, 2H), 7.43 – 7.38 (m, 3H), 7.12 – 7.09 (m, 1H),

5.21 (d, $J = 8.6$ Hz, 1H), 3.71 – 3.64 (m, 1H), 1.65 – 1.54 (m, 3H), 1.45 – 1.38 (m, 1H), 1.34 – 1.30 (m, 1H), 1.08 – 0.97 (m, 4H), 0.78 – 0.70 (m, 1H), 0.60 (ddd, $J = 14.8, 11.8, 5.2$ Hz, 1H), 0.54 (d, $J = 6.7$ Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ (ppm) = 164.8, 140.7, 140.7 (q, $J = 38.5$ Hz), 135.9, 131.5, 131.4, 130.9, 130.0, 129.6, 126.5, 124.5, 121.7, 119.0 (q, $J = 272.0$ Hz), 111.4, 49.9, 42.8, 28.9, 28.6, 26.3, 26.1, 26.1, 17.0. HRMS (ESI) m/z calc. for $\text{C}_{23}\text{H}_{25}\text{F}_3\text{N}_3\text{O}$ $[\text{M}^+\text{H}]^+$ 416.1950, found 416.1944. $[\alpha]_D^{22}$: +41.67° ($c = 0.12$ MeOH).

(P)-(S)-N-(2-Hydroxy-1-phenylethyl)-2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzamide (P)-44

From 40 mg of (P)-1 and (S)-(+)-2-Phenylglycinol, 41 mg of oil (74%). ^1H NMR (400 MHz, CDCl_3) δ 7.93 – 7.85 (m, 2H), 7.70 – 7.64 (m, 2H), 7.41 (dddd, $J = 13.4, 8.6, 6.1, 2.8$ Hz, 3H), 7.25 – 7.20 (m, 3H), 7.12 (dd, $J = 6.9, 1.8$ Hz, 1H), 6.23 (d, $J = 7.1$ Hz, 1H), 4.79 (dt, $J = 7.3, 4.6$ Hz, 1H), 3.48 – 3.39 (m, 1H), 3.27 (dd, $J = 11.0, 4.1$ Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 165.5, 140.9 (q, $J = 38.1$ Hz), 140.6, 138.4, 137.4, 134.9, 131.9, 131.6, 130.9, 130.0, 129.6, 128.5, 128.0, 126.5, 124.5, 121.65, 119.0 (q, $J = 272.2$ Hz), 111.4, 65.6, 55.6 ^{19}F NMR (376 MHz, CDCl_3) δ -61.29 HRMS (ESI) m/z : $[\text{M}^+\text{H}]^+$ calculated for $\text{C}_{23}\text{H}_{19}\text{O}_2\text{N}_3\text{F}_3$: 426.1424, found: 426.1423, $[\alpha]_D^{24} = -32.50^\circ$ ($c = 0.76$, MeOH).

(M)-(S)-N-(2-Hydroxy-1-phenylethyl)-2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzamide (M)-44

From 40 mg of (M)-1 and (S)-(+)-2-Phenylglycinol, 39 mg of oil (70%). ^1H NMR (400 MHz, CDCl_3) δ 7.91 (td, $J = 8.3, 1.1$ Hz, 2H), 7.70 – 7.63 (m, 2H), 7.45 – 7.39 (m, 2H), 7.36 (dt, 1H), 7.18 – 7.11 (m, 1H), 7.07 (d, $J = 8.1$ Hz, 2H), 6.71 (dd, $J = 7.8, 1.5$ Hz, 2H), 6.12 (d, $J = 6.9$ Hz, 1H), 4.79 (dt, $J = 6.9, 5.0$ Hz, 1H), 3.55 (dd, $J = 5.4, 11.2$ Hz, 1H), 3.51 (dd, $J = 4.6, 11.2$ Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 165.4, 141.0 (q, $J = 38.7$ Hz), 140.8, 140.8, 138.1, 137.4, 134.8, 132.0, 131.55, 130.95, 130.3, 129.6, 128.9, 127.9, 126.5, 126.4, 124.5, 121.8, 119.5 (q, $J = 272.7$ Hz), 111.2, 65.8, 55.95 ^{19}F NMR (376 MHz, CDCl_3) δ -61.36 HRMS (ESI) m/z : $[\text{M}^+\text{H}]^+$ calculated for $\text{C}_{23}\text{H}_{19}\text{O}_2\text{N}_3\text{F}_3$: 426.1424, found: 426.1423, $[\alpha]_D^{25} = +130.50^\circ$ ($c = 0.8$ MeOH).

(P)-(R)-N-(2-hydroxy-1-phenylethyl)-2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzamide (P)-45:

From 40 mg of (P)-1 and (R)-(+)-2-Phenylglycinol, 46 mg of white foam (83%). ^1H NMR (500 MHz, CDCl_3) δ 7.96 – 7.91 (m, 1H), 7.71 – 7.66 (m, 1H), 7.46 – 7.41 (m, 1H), 7.37 (t, $J = 7.7$ Hz, 1H), 7.21 – 7.13 (m, 2H), 7.08 (d, $J = 8.1$ Hz, 1H), 6.73 – 6.69 (m, 1H), 6.06 (d, $J = 6.8$ Hz, 1H), 4.83 – 4.79 (m, 1H), 3.55 (qd, $J = 11.2, 4.9$ Hz, 1H). ^{13}C NMR (126 MHz, CDCl_3) δ 165.46 (s), 141.0 (q, $J = 38.5$ Hz), 140.8 – 140.76 (m), 138.05 (s), 137.4 (s), 134.8 (s), 132.1 (s), 131.5 (s), 131.0 (s), 130.3 (s), 129.6 (s), 128.9 (s), 128.0 (s), 126.5 (s), 126.4 (s), 124.6 (s), 121.9 (s), 118.9 (q, $J = 271.9$ Hz), 111.2 (s), 65.9 (s), 56.0 (s). ^{19}F NMR (471 MHz, CDCl_3) δ -61.36 (s). HRMS (ESI) $[\text{M}^+\text{H}]^+$ calculated for $\text{C}_{23}\text{H}_{18}\text{O}_2\text{N}_3\text{F}_3+\text{H}$: 426.1424, found: 426.1427, $[\alpha]_D^{25} = -138.50^\circ$ ($c = 0.12$ MeOH).

(M)-(R)-N-(2-hydroxy-1-phenylethyl)-2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzamide (M)-45

From 40 mg of (M)-1 and (R)-(+)-2-Phenylglycinol, 38 mg of white foam (70%). ^1H NMR (500 MHz, CDCl_3) δ 7.90 (d, $J = 7.5$ Hz, 1H), 7.89 – 7.86 (m, 1H), 7.70 – 7.65 (m, 2H), 7.46 – 7.36 (m, 3H), 7.25 – 7.20 (m, 3H), 7.12 (d, $J = 7.3$ Hz, 1H), 6.98 – 6.94 (m, 2H), 6.25 (d, $J = 7.2$ Hz, 1H), 4.79 (dt, $J = 7.4, 4.6$ Hz, 1H), 3.44 (dd, $J = 11.1, 5.0$ Hz, 2H), 3.26 (dd, $J = 11.1, 4.2$ Hz, 1H). ^{13}C NMR (126 MHz, CDCl_3) δ 165.5 (s), 140.8 (q, $J = 38.3$ Hz), 140.6 (s), 138.4 (s), 137.4 (s), 134.9 (s), 132.0 (s), 131.6 (s), 130.9 (s), 130.05 (s), 129.6 (s), 128.9 (s), 128.8 (s), 128.0 (s), 127.9 (s), 126.7 (s), 126.5 (s), 124.6 (s), 121.6 (s), 119.0 (q, $J = 271.9$ Hz), 111.4 (s), 65.6 (s), 55.6 (s). ^{19}F NMR (471 MHz, CDCl_3) δ -61.31 (s). HRMS (ESI) $[\text{M}^+\text{H}]^+$ calculated for $\text{C}_{23}\text{H}_{18}\text{O}_2\text{N}_3\text{F}_3+\text{H}$: 426.1424, found: 426.1427, $[\alpha]_D^{22} = +35.84^\circ$ ($c = 0.12$, MeOH).

(P)-(S)-N-(1-Hydroxy-3-methylbutan-2-yl)-2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzamide (P)-46

From 40 mg of (P)-1 and (S)-(+)-2-amino-3-methylbutanol, 21 mg of white solid (41%) after purification by preparative HPLC. ¹H NMR (400 MHz, CDCl₃) δ 7.94 – 7.90 (m, 1H), 7.89 – 7.85 (m, 1H), 7.71 – 7.64 (m, 2H), 7.45 – 7.38 (m, 3H), 7.15 – 7.09 (m, 1H), 5.70 (d, *J* = 8.6 Hz, 1H), 3.53 (ddd, *J* = 11.6, 8.5, 4.2 Hz, 1H), 3.24 (dd, *J* = 11.0, 4.6 Hz, 1H), 2.96 (dd, *J* = 11.0, 3.7 Hz, 1H), 1.63 (dq, *J* = 13.7, 6.9 Hz, 1H), 0.72 (d, *J* = 6.8 Hz, 3H), 0.67 (d, *J* = 6.8 Hz, 3H). ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 165.9, 141.0, 140.6, 137.4, 135.4, 131.8, 131.3, 130.9, 130.0, 129.5, 126.6, 124.6, 121.5, 119.0 (q, *J* = 272.0 Hz), 111.5, 62.8, 56.8, 28.8, 19.3, 18.5. ¹⁹F NMR (376 MHz, CDCl₃) δ -61.18. HRMS (ESI) *m/z*: [M+H]⁺ calculated for C₂₀H₂₁O₂N₃F₃: 392.1580, found: 392.1577, [α]_D²² = +99.6° (c = 0.25, MeOH).

(M)-(S)-N-(1-Hydroxy-3-methylbutan-2-yl)-2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzamide (M)-46

From 40 mg of (M)-1 and (S)-(+)-2-amino-3-methylbutanol, 22 mg of a white solid (41%) after purification by preparative HPLC. ¹H NMR (400 MHz, CDCl₃) δ 7.96 – 7.90 (m, 1H), 7.90 – 7.84 (m, 1H), 7.70 – 7.63 (m, 2H), 7.46 – 7.36 (m, 3H), 7.14 – 7.08 (m, 1H), 5.65 (d, *J* = 8.4 Hz, 1H), 3.60 – 3.52 (m, 1H), 3.33 (ddd, *J* = 15.0, 11.1, 4.5 Hz, 2H), 1.53 (dq, *J* = 13.6, 6.8 Hz, 1H), 0.53 (d, *J* = 6.8 Hz, 3H). ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 166.1, 141.1 (q, *J* = 38.5 Hz), 140.8, 137.5, 135.4, 131.8, 131.4, 130.9, 129.9, 129.6, 126.4, 124.5, 118.9 (q, *J* = 272.1 Hz), 111.2, 63.0, 57.0, 28.7, 19.1, 18.14. ¹⁹F NMR (376 MHz, CDCl₃) δ -61.36. HRMS (ESI) *m/z*: [M+H]⁺ calculated for C₂₀H₂₁O₂N₃F₃: 392.1580, found: 392.1581, [α]_D²² = +81.63° (c = 0.49, MeOH).

(P)-(R)-N-(1-hydroxy-3-methylbutan-2-yl)-2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzamide (P)-47

From 40 mg of (P)-I and (R)-(-)-2-amino-3-methylbutanol, 30 mg of yellow oil (60 %) after purification by preparative HPLC. ¹H NMR (500 MHz, CDCl₃) δ 7.93 (dd, *J* = 6.5, 2.3 Hz, 1H), 7.88 (dd, *J* = 6.0, 3.3 Hz, 1H), 7.70 – 7.65 (m, 2H), 7.45 – 7.37 (m, 4H), 7.11 (dd, *J* = 6.5, 2.3 Hz, 1H), 5.64 (d, *J* = 8.3 Hz, 1H), 3.60 – 3.53 (m, 1H), 3.38 (dd, *J* = 11.1, 5.2 Hz, 1H), 3.29 (dd, *J* = 11.1, 3.8 Hz, 1H), 1.53 (dq, *J* = 13.6, 6.8 Hz, 1H), 0.62 (d, *J* = 6.8 Hz, 3H), 0.53 (d, *J* = 6.8 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 166.0 (s), 141.1 (q, *J* = 38.8 Hz), 140.8(s), 137.4 (s), 135.3 (s), 131.8 (s), 131.4 (s), 130.9 (s), 129.9 (s), 129.6 (s), 126.3 (s), 124.5 (s), 121.8 (s), 118.9 (q, *J* = 272.2 Hz), 111.2 (s), 63.1 (s), 57.0 (s), 28.7 (s), 19.05 (s), 18.14 (s). ¹⁹F NMR (471 MHz, CDCl₃) δ -61.36 (s). HRMS (ESI) [M+H]⁺ calculated for C₂₀H₂₀O₂N₃F₃+H: 392.1580, found: 392.1579, [α]_D²² = -86.0° (c = 0.3, MeOH).

(M)-(R)-N-(1-hydroxy-3-methylbutan-2-yl)-2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzamide (M)-47

From 40 mg of (M)-I and (R)-(-)-2-amino-3-methylbutanol, 25 mg of white solid (50 %) after purification by preparative HPLC. ¹H NMR (500 MHz, CDCl₃) δ 7.91 (dd, *J* = 6.6, 2.1 Hz, 1H), 7.87 – 7.84 (m, 1H), 7.69 – 7.64 (m, 2H), 7.45 – 7.36 (m, 3H), 7.11 (dd, *J* = 6.6, 2.1 Hz, 1H), 5.77 (d, *J* = 8.7 Hz, 1H), 3.52 (ddd, *J* = 12.4, 8.5, 4.2 Hz, 1H), 3.25 (dd, *J* = 10.9, 4.6 Hz, 1H), 2.97 (dd, *J* = 11.0, 3.7 Hz, 1H), 1.63 (dq, *J* = 13.7, 6.9 Hz, 1H), 0.71 (d, *J* = 6.8 Hz, 3H), 0.65 (d, *J* = 6.8 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 165.9 (s), 140.8 (q, *J* = 38.3 Hz), 140.6 (s), 137.4 (s), 135.4 (s), 131.75 (s), 131.3 (s), 130.9 (s), 129.9 (s), 129.5 (s), 126.5 (s), 124.6 (s), 121.5 (s), 119.0 (q, *J* = 271.9 Hz), 111.5 (s), 62.7 (s), 56.7 (s), 28.8 (s), 19.3 (s), 18.5 (s). ¹⁹F NMR (471 MHz, CDCl₃) δ -61.24 (s). HRMS (ESI) [M+H]⁺ calculated for C₂₀H₂₀O₂N₃F₃+H: 392.1580, found: 392.1585, [α]_D²² = -104.76° (c = 0.21, MeOH).

(P)-Methyl (2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoyl)-D-alaninate (P)-48

From 40 mg of (P)-1, D-AlaOMe.HCl and 1.1 eq of triethylamine. 25 mg of white solid (50 %). ¹H NMR (500 MHz, CDCl₃) δ 7.92 (dd, *J* = 6.5, 2.4 Hz, 1H), 7.86 (dd, *J* = 5.7, 3.6 Hz, 1H), 7.71 – 7.66 (m, 2H), 7.48 – 7.44 (m, 1H), 7.42 – 7.35 (m, 2H), 7.09 (dd, *J* = 6.5, 2.4 Hz, 1H), 6.12 (d, *J* = 6.9 Hz, 1H), 4.35 (p, *J* = 7.1 Hz, 1H), 3.65 (s, 3H), 0.85 (d, *J* = 7.2 Hz, 3H). ¹³C{¹H} NMR (126 MHz, CDCl₃)

δ 172.7, 164.7, 140.6 (q, $J = 38.6$ Hz), 134.7, 132.0, 131.8, 130.9, 129.75, 129.6, 126.4, 124.4, 121.6, 119.0 (q, $J = 272.1$ Hz), 111.5, 52.7, 48.3, 17.7. ^{19}F NMR (471 MHz, CDCl_3) δ -61.26 HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{19}\text{H}_{17}\text{O}_3\text{N}_3\text{F}_3$: 392.1217, found: 392.1211, $[\alpha]_D^{22} = -59.03^\circ$ ($c = 0.31$ MeOH).

(M)-Methyl (2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoyl)-D-alaninate (M)-48

From 40 mg of (M)-1, D-AlaOMe.HCl and 1.1 eq of triethylamine. 30 mg of white solid (60 %). ^1H NMR (500 MHz, CDCl_3) δ 7.95 – 7.90 (m, 1H), 7.87 – 7.83 (m, 1H), 7.70 – 7.66 (m, 2H), 7.47 – 7.43 (m, 1H), 7.42 – 7.36 (m, 2H), 7.09 (dd, $J = 5.8, 3.3$ Hz, 1H), 6.10 (d, $J = 6.9$ Hz, 1H), 4.35 (p, $J = 7.1$ Hz, 1H), 3.59 (s, 3H), 1.03 (d, $J = 7.0$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 172.6, 164.6, 141.2 (q, $J = 38.7$ Hz), 140.7, 137.55, 134.7, 132.0, 132.0, 130.9, 129.7, 129.7, 126.3, 124.4, 121.7, 118.9 (q, $J = 272.1$ Hz), 111.1, 52.6, 48.35, 18.1 ^{19}F NMR (471 MHz, CDCl_3) δ -61.63 HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{19}\text{H}_{17}\text{O}_3\text{N}_3\text{F}_3$: 392.1217, found: 392.1219, $[\alpha]_D^{22} = +142.09^\circ$ ($c = 0.24$ MeOH).

(P)-methyl (2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoyl)-L-alaninate (P)-49

From 40 mg of (P)-1, L-AlaOMe.HCl and 1.1 eq. of triethylamine, 16 mg of white solid (33 %) after purification by preparative HPLC. ^1H NMR (400 MHz, CDCl_3) δ 7.95 – 7.90 (m, 1H), 7.87 – 7.83 (m, 1H), 7.71 – 7.65 (m, 2H), 7.47 – 7.43 (m, 1H), 7.42 – 7.36 (m, 2H), 7.11 – 7.06 (m, 1H), 6.10 (d, $J = 7.0$ Hz, 1H), 4.41 – 4.29 (m, 1H), 3.59 (s, 3H), 1.03 (d, $J = 7.1$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 172.6 (s), 164.6 (s), 141.1 (q, $J = 38.5$ Hz), 140.7 (s), 137.5 (s), 134.7 (s), 131.99 (s), 131.96 (s), 130.8 (s), 129.7 (s), 129.6 (s), 126.3 (s), 124.3 (s), 121.7 (s), 118.9 (q, $J = 272.2$ Hz), 111.18 (s), 52.6 (s), 48.3 (s), 18.1 (s). ^{19}F NMR (376 MHz, CDCl_3) δ -61.63 (s). HRMS (ESI) $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{19}\text{H}_{16}\text{O}_3\text{N}_3\text{F}_3+\text{H}$: 392.1217, found: 392.1213, $[\alpha]_D^{22} = -138.71^\circ$ ($c = 0.31$ MeOH).

(M)-methyl (2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoyl)-L-alaninate (M)-49

From 40 mg of (M)-1, L-AlaOMe.HCl and 1.1 eq. of triethylamine. 18 mg of white solid (36%). ^1H NMR (400 MHz, CDCl_3) δ 7.91 (dd, $J = 6.2, 2.8$ Hz, 1H), 7.85 (dd, $J = 5.8, 3.5$ Hz, 1H), 7.71 – 7.65 (m, 2H), 7.47 – 7.43 (m, 1H), 7.42 – 7.34 (m, 2H), 7.08 (dd, $J = 6.0, 3.0$ Hz, 1H), 6.14 (d, $J = 6.8$ Hz, 1H), 4.34 (p, $J = 7.1$ Hz, 1H), 3.64 (s, 3H), 0.85 (d, $J = 7.1$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 172.7 (s), 164.7 (s), 140.6 (q, $J = 38.5$ Hz), 140.6 (s), 137.6 (s), 134.7 (s), 132.0 (s), 131.8 (s), 130.9 (s), 129.7 (s), 129.6 (s), 126.3 (s), 124.4 (s), 121.6 (s), 119.0 (q, $J = 271.8$ Hz), 111.5 (s), 52.7 (s), 48.3 (s), 17.7 (s). ^{19}F NMR (376 MHz, CDCl_3) δ -61.25 (s). HRMS ESI $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{19}\text{H}_{16}\text{O}_3\text{N}_3\text{F}_3+\text{H}$: 392.1217, found: 392.1221, $[\alpha]_D^{22} = +55.06^\circ$ ($c = 0.18$ MeOH).

(P)-methyl (2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoyl)-L-phenylalaninate (P)-50

From 15 mg of (P)-1 and L-PheOMe.HCl and 2.2 eq. of triethylamine, 17,5 mg of oil (75 %). Purified by column chromatography (hexane: ethyl acetate 3:1, column dimensions 1x10 cm). ^1H NMR (500 MHz, CDCl_3) δ 7.94 – 7.91 (m, 1H), 7.70 – 7.63 (m, 5H), 7.43 – 7.36 (m, 5H), 7.25 – 7.22 (m, 4H), 7.09 – 7.06 (m, 1H), 6.94 (dd, $J = 7.3, 2.1$ Hz, 3H), 6.10 (d, $J = 7.5$ Hz, 1H), 4.68 (dt, $J = 7.6, 5.8$ Hz, 1H), 3.58 (s, 4H), 2.91 (dd, $J = 5.8, 2.2$ Hz, 3H). ^{13}C NMR { ^1H } (126 MHz, CDCl_3) δ 171.2, 164.8, 141.0 (q, $J = 39.6$ Hz), 140.7, 137.8, 135.6, 134.6, 132.3, 132.0, 130.8, 130.0, 129.3, 129.2, 128.7, 127.3, 126.2, 124.3, 121.6, 119.0 (q, $J = 271.5$ Hz), 111.4, 53.5, 52.5, 37.8. ^{19}F NMR (376 MHz, CDCl_3) δ = -61.58., HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{25}\text{H}_{21}\text{F}_3\text{N}_3\text{O}_3$: 468.1535 found: 468.1529, $[\alpha]_D^{22} = -75.00^\circ$ ($c = 0.12$ MeOH).

(M)-methyl (2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoyl)-L-phenylalaninate (M)-50

From 15 mg of (M)-1 and L-PheOMe.HCl and 2.2 eq. of triethylamine, 19 mg of oil (81 %). Purified by column chromatography (hexane: ethyl acetate 3:1, column dimensions 1x10 cm). ^1H NMR (500 MHz, CDCl_3) δ 7.93 (d, $J = 7.8$ Hz, 1H), 7.76 – 7.74 (m, 1H), 7.69 – 7.63 (m, 2H), 7.43 – 7.33 (m, 4H), 7.25 – 7.20 (m, 3H), 7.03 (d, $J = 7.9$ Hz, 1H), 6.90 (dd, $J = 7.3, 2.0$ Hz, 2H), 6.04 (d, $J = 7.5$ Hz, 1H), 4.65 (dt, $J = 7.6, 6.1$ Hz, 1H), 3.59 (s, 3H), 2.84 – 2.75 (m, 2H). ^{13}C NMR { ^1H } (126 MHz, CDCl_3) δ 171.5, 164.9, 141.1 (q, $J = 38.5$ Hz), 140.7, 137.6, 135.5, 134.4, 132.2, 132.1, 130.8, 130.0, 129.5, 129.1, 128.8, 127.3, 127.3, 126.2, 124.3, 121.7, 119.0 (q, $J = 272.2$ Hz), 111.3., 53.6, 52.4, 37.8., ^{19}F NMR

(376 MHz, CDCl₃) δ (ppm) = -61.43, **HRMS** (ESI) m/z : [M+H]⁺ calculated for C₂₅H₂₁F₃N₃O₃: 468.1535 found: 468.1528, $[\alpha]_D^{22} = +33.00^\circ$ (c= 0.09 MeOH).

General procedure for TBBA-ester formation

(P)-(S)-1-Methoxy-1-oxopropan-2-yl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (P)-54: (*P*)-1-Carboxyphenyl(2-trifluoromethyl)benzimidazole (**P**)-**1** (40 mg; 0.13 mmol; 1 eq) and (–)-methyl L-lactate (13 μ L; 14 mg; 0.13 mmol; 1 eq) were dissolved in dry DCM (2 mL). DCC (27 mg; 0.13 mmol; 1 eq) and then DMAP (16 mg; 0.13 mmol; 1 eq) were subsequently added into the solution. The solution was then stirred at room temperature for 16 hours. After 16 hours, a solid precipitate was filtered-off via syringe filter. The mixture was then adsorbed on celite and purified via column chromatography (hexane: ethyl acetate 6:1, column dimensions: 1x10 cm). 46 mg of white foamy solid (88 %) **¹H NMR** (400 MHz, CDCl₃) δ 8.32 – 8.28 (m, 1H), 7.93 – 7.88 (m, 1H), 7.79 (td, $J = 7.6, 1.7$ Hz, 1H), 7.72 (td, $J = 7.7, 1.4$ Hz, 1H), 7.49 (dd, $J = 7.7, 1.2$ Hz, 1H), 7.41 – 7.33 (m, 2H), 7.05 – 7.00 (m, 1H), 4.91 (q, $J = 7.1$ Hz, 0H), 3.49 (s, 2H), 0.99 (d, $J = 5.2$ Hz, 1H). **¹³C{¹H} NMR** (101 MHz, CDCl₃) δ 170.2, 163.6, 141.2, 140.8, 140.7, 137.9, 134.1, 134.1, 133.1, 130.8, 130.3, 128.7, 125.9, 124.0, 121.3, 120.3, 117.6, 69.6, 52.3, 16.3 **¹⁹F NMR** (376 MHz, CDCl₃) δ -62.03 **HRMS** (ESI) m/z : [M+H]⁺ calculated for C₁₉H₁₆O₄N₂F₃: 393.1057 found: 393.1058, $[\alpha]_D^{22} = -36.7^\circ$ (c= 0.46 CHCl₃).

(P)-(R)-1-phenylethyl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (P)-51 Using general procedure, from 15 mg of (**P**)-**1** and (*R*)-1-Phenylethanol, 18 mg of oil (88 %). Purified by column chromatography (hexane: ethyl acetate 10:1, column dimensions 1x10 cm). **¹H NMR** (400 MHz, CDCl₃) δ 8.23 – 8.19 (m, 1H), 7.98 – 7.93 (m, 1H), 7.75 (td, $J = 7.6, 1.8$ Hz, 1H), 7.68 (td, $J = 7.6, 1.4$ Hz, 1H), 7.48 – 7.44 (m, 1H), 7.44 – 7.38 (m, 1H), 7.38 – 7.33 (m, 1H), 7.29 – 7.24 (m, 4H), 7.07 – 7.02 (m, 2H), 7.02 – 6.98 (m, 1H), 5.68 (q, $J = 6.6$ Hz, 1H), 0.80 (d, $J = 6.6$ Hz, 3H). **¹³C NMR {¹H}** (101 MHz, CDCl₃) δ 163.9, 140.9 (q, $J = 38.4$ Hz), 140.7, 140.2, 137.8, 133.6, 133.5, 132.7, 130.6, 130.0, 129.8, 128.5, 128.2, 126.4, 126.0, 124.0, 121.5, 118.9 (q, $J = 272.2$ Hz), 110.9, 74.1, 20.5, **¹⁹F NMR** (376 MHz, CDCl₃) δ (ppm) = -62.00, **HRMS** (ESI-TOF) m/z : [M+H]⁺ calculated for C₂₃H₁₈F₃N₂O₂: 411.1320 found: 411.1317, $[\alpha]_D^{22} = -131.18^\circ$ (c= 0.17 CHCl₃).

(M)-(R)-1-phenylethyl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (M)-51 Using general procedure, from 15 mg of (**M**)-**1** and (*R*)-1-Phenylethanol, 19 mg of oil (93 %). Purified by column chromatography (hexane: ethyl acetate 10:1, column dimensions 1x10 cm). **¹H NMR** (400 MHz, CDCl₃) δ 8.28 – 8.25 (m, 1H), 7.96 (dt, $J = 8.1, 1.0$ Hz, 1H), 7.75 (td, $J = 7.6, 1.8$ Hz, 1H), 7.69 (td, $J = 7.6, 1.4$ Hz, 1H), 7.47 – 7.41 (m, 2H), 7.34 (ddd, $J = 8.3, 7.2, 1.1$ Hz, 1H), 7.16 – 7.11 (m, 1H), 7.06 (ddt, $J = 8.3, 6.6, 1.4$ Hz, 2H), 6.97 – 6.93 (m, 1H), 6.58 – 6.54 (m, 2H), 5.74 (q, $J = 6.7$ Hz, 1H), 1.11 (d, $J = 6.7$ Hz, 3H). **¹³C NMR {¹H}** (101 MHz, CDCl₃) δ 163.8, 141.1 (q, $J = 38.6$ Hz), 140.8, 140.4, 138.0, 133.7, 133.2, 130.7, 130.2, 129.9, 128.4, 128.0, 126.1, 126.0, 124.1, 121.6, 119.0 (q, $J = 272.2$ Hz), 111.2, 74.2, 21.3, **¹⁹F NMR** (376 MHz, CDCl₃) δ (ppm) = -62.02, **HRMS** (ESI-TOF) m/z : [M+H]⁺ calculated for C₂₃H₁₈F₃N₂O₂: 411.1320 found: 411.1317, $[\alpha]_D^{22} = +3.64^\circ$ (c= 0.11 CHCl₃).

(P)-(S)-sec-butyl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (P)-52 Using general procedure, from 15 mg of (**P**)-**1** and (*S*)-(+)-2-Butanol, 11.5 mg of oil (64 %). Purified by column chromatography (hexane: ethyl acetate 9:1, column dimensions 1x10 cm). **¹H NMR** (400 MHz, CDCl₃) δ 8.28 (dd, $J = 7.6, 1.8$ Hz, 1H), 7.94 (d, $J = 7.8$ Hz, 1H), 7.74 (dq, $J = 15.0, 7.5, 1.6$ Hz, 2H), 7.48 (dd, $J = 7.6, 1.2$ Hz, 1H), 7.37 (tdd, $J = 15.0, 7.3, 1.1$ Hz, 2H), 6.99 (d, $J = 7.5$ Hz, 1H), 4.73 – 4.63 (m, 1H), 0.88 (d, $J = 6.3$ Hz, 3H), 0.87 – 0.80 (m, 1H), 0.77 – 0.64 (m, 1H), 0.35 (t, $J = 7.5$ Hz, 3H). **¹³C NMR {¹H}** (101 MHz, CDCl₃) δ 164.1, 141.1 (q, $J = 39.4$ Hz), 140.7, 138.1, 133.7, 133.5, 132.9, 130.7, 130.2, 125.9, 124.0, 121.5, 119.0 (q, $J = 271.9$ Hz), 111.1, 74.2, 28.1, 18.9, 9.4, **¹⁹F NMR** (376 MHz, CDCl₃) δ (ppm) = -62.04. **HRMS** (ESI) m/z : [M+H]⁺ calculated for C₁₉H₁₈F₃N₂O₂: 363.1320 found: 363.1313, $[\alpha]_D^{22} = -88.57^\circ$ (c= 0.07 CHCl₃).

(M)-(S)-sec-butyl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (M)-52 Using general procedure, from 15 mg of (M)-1 and (S)-(+)-2-Butanol, 10 mg of oil (55 %). Purified by column chromatography (hexane: ethyl acetate 9:1, column dimensions 1x10 cm). ¹H NMR (400 MHz, CDCl₃) δ 8.25 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.94 (d, *J* = 7.9 Hz, 1H), 7.76 (td, *J* = 7.6, 1.8 Hz, 1H), 7.71 (td, *J* = 7.6, 1.4 Hz, 1H), 7.49 (d, *J* = 7.5 Hz, 1H), 7.42 – 7.30 (m, 1H), 6.97 (d, *J* = 7.9 Hz, 1H), 4.73 – 4.54 (m, 1H), 1.29 – 1.07 (m, 1H), 0.68 (t, *J* = 7.4 Hz, 1H), 0.39 (d, *J* = 6.3 Hz, 1H). ¹³C NMR {1H} (101 MHz, CDCl₃) δ 164.3, 141.1 (q, *J* = 38.6 Hz), 140.7, 138.0, 133.6, 133.5, 132.8, 130.7, 130.2, 130.0, 126.0, 124.1, 121.5, 119.0 (q, *J* = 271.9 Hz), 111.0, 74.2, 28.3, 18.1, 9.7. ¹⁹F NMR (376 MHz, CDCl₃) δ = -61.86. HRMS (ESI-TOF) m/z: [M+H]⁺ calculated for C₁₉H₁₈F₃N₂O₂: 363.1320 found: 363.1315, [α]_D²² = +141.67°(c= 0.06 CHCl₃).

(P)-(S)-but-3-yn-2-yl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (P)-53 Using general procedure, from 15 mg of (P)-1 and (S)-But-3-yn-2-nol, 15 mg of oil (84 %). Purified by column chromatography (hexane: ethyl acetate 7:1, column dimensions 1x10 cm). ¹H NMR (400 MHz, CDCl₃) δ 8.26 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.94 (d, *J* = 7.8 Hz, 1H), 7.76 (dtd, *J* = 15.2, 7.6, 1.0 Hz, 2H), 7.50 (d, *J* = 7.7 Hz, 1H), 7.37 (td, *J* = 14.3, 7.2 Hz, 2H), 6.99 (d, *J* = 8.1 Hz, 1H), 5.21 (qd, *J* = 6.7, 2.0 Hz, 1H), 2.07 (d, *J* = 2.1 Hz, 1H), 1.08 (d, *J* = 6.8 Hz, 3H). ¹³C NMR {1H} (101 MHz,) δ 163.4, 141.0 (q, *J* = 39.1 Hz), 140.8, 138.0, 134.0, 133.9, 132.8, 130.7, 130.2, 129.3, 126.0, 124.0, 121.6, 119.0 (q, *J* = 271.9 Hz), 111.0, 80.6, 73.1, 61.4, 20.5. ¹⁹F NMR (376 MHz, CDCl₃) δ = -61.99. HRMS (ESI) m/z: [M+H]⁺ calculated for C₁₉H₁₄F₃N₂O₂: 359.1007 found: 359.1001, [α]_D²² = -156.67°(c= 0.09 CHCl₃).

(M)-(S)-but-3-yn-2-yl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (M)-53 Using general procedure, from 15 mg of (M)-1 and (S)-But-3-yn-2-nol, 16 mg of oil (89 %). Purified by column chromatography (hexane: ethyl acetate 7:1, column dimensions 1x10 cm). ¹H NMR (400 MHz, CDCl₃) δ 8.27 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.95 (d, *J* = 7.6 Hz, 1H), 7.76 (dtd, *J* = 25.7, 7.5, 1.5 Hz, 2H), 7.50 (d, *J* = 7.5 Hz, 1H), 7.40 (td, *J* = 7.3, 7.3, 1.3 Hz, 1H), 7.35 (td, *J* = 8.1, 1.3 Hz, 1H), 6.97 (dd, *J* = 7.4, 0.9 Hz, 1H), 5.19 (qd, *J* = 6.7, 2.1 Hz, 1H), 2.35 (d, *J* = 2.2 Hz, 1H), 0.82 (d, *J* = 6.7 Hz, 4H). ¹³C NMR {1H} (101 MHz, CDCl₃) δ 163.4, 141.2 (q, *J* = 38.6 Hz), 140.8, 137.9, 134.00 (s), 133.93 (s), 132.8, 130.7, 130.2, 129.3, 126.0, 124.0, 121.6, 119.0 (q, *J* = 272.0 Hz), 110.8, 80.9, 73.5, 61.4, 20.1. ¹⁹F NMR (376 MHz, CDCl₃) δ = -62.06. HRMS (ESI-TOF) m/z: [M+H]⁺ calculated for C₁₉H₁₄F₃N₂O₂: 359.1000 found: 359.1001, [α]_D²² = -61.25°(c= 0.08 CHCl₃).

(M)-(S)-1-Methoxy-1-oxopropan-2-yl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (M)-54: (M)-1-Carboxyphenyl(2-trifluoromethyl)benzimidazole (M)-1 (40 mg, 0.13 mmol, 1 eq) and (-)-methyl L-lactate (13 μL, 14 mg, 0.13 mmol, 1 eq) purified via column chromatography (hexane: ethyl acetate 6:1, column dimensions: 1x10 cm). 43 mg of a white foamy solid (85 %). ¹H NMR (400 MHz, CDCl₃) δ 8.31 – 8.25 (m, 1H), 7.95 – 7.89 (m, 1H), 7.80 (td, *J* = 7.6, 1.7 Hz, 1H), 7.73 (td, *J* = 7.7, 1.4 Hz, 1H), 7.50 (d, *J* = 7.7 Hz, 1H), 7.43 – 7.30 (m, 1H), 7.01 – 6.95 (m, 1H), 4.86 (q, *J* = 7.1 Hz, 1H), 3.61 (s, 2H), 0.82 (d, *J* = 7.1 Hz, 1H). ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 170.2, 163.7, 141.1 (q, *J* = 38.6 Hz), 140.6, 137.9, 134.1, 134.0, 133.0, 130.8, 130.3, 128.8, 125.9, 124.0, 121.5, 118.9 (q, *J* = 271.9 Hz), 111.0, 69.5, 52.4, 16.0. ¹⁹F NMR (376 MHz, CDCl₃) δ -61.98. HRMS (ESI) m/z: [M+H]⁺ calculated for C₁₉H₁₆O₄N₂F₃: 393.1057 found: 393.1057, [α]_D²² = +68.14° (c= 0.43 CHCl₃).

(P)-(S)-2-methoxy-2-oxo-1-phenylethyl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (P)-55 Using general procedure, from 20 mg of (P)-1 and Methyl-(S)-(+)-mandelate, 22 mg of white solid (75 %). Purified by column chromatography (hexane: ethyl acetate 7:1, column dimensions 1x10 cm). ¹H NMR (400 MHz, CDCl₃) δ 8.36 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.84 – 7.80 (m, *J* = 2.5, 1.7 Hz, 1H), 7.78 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.73 (td, *J* = 7.6, 1.4 Hz, 1H), 7.44 (dd, *J* = 7.6, 1.0 Hz, 1H), 7.40 – 7.31 (m, 3H), 7.28 – 7.22 (m, 3H), 7.03 – 6.97 (m, 3H), 5.79 (s, 1H), 3.58 (s, 3H). ¹³C NMR {1H} (101 MHz, CDCl₃) δ 168.5, 163.8, 140.9 (q, *J* = 38.9 Hz), 140.7, 137.6, 134.10, 134.07, 132.8, 130.7, 130.3, 129.4, 128.8, 128.7, 127.7, 126.7, 125.9, 123.9, 121.6, 118.9 (q, *J* = 271.7 Hz), 110.9, 75.5, 52.7. ¹⁹F NMR (376 MHz, CDCl₃) δ -62.10. HRMS (ESI-TOF) m/z: [M+H]⁺ calculated for C₂₄H₁₈F₃N₂O₄: 455.1213 found: 455.1230, [α]_D²² = +32.73°(c= 0.22 CHCl₃).

(M)-(S)-2-methoxy-2-oxo-1-phenylethyl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (M)-55 Using general procedure, from 20 mg of **(M)-1** and Methyl-(S)-(+)-mandelate, 24 mg of white solid (82 %). Purified by column chromatography (hexane: ethyl acetate 7:1, column dimensions 1x10 cm). ¹H NMR (400 MHz, CDCl₃) δ 8.32 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.78 (td, *J* = 7.6, 1.7 Hz, 1H), 7.72 (td, *J* = 7.6, 1.4 Hz, 1H), 7.45 (d, *J* = 7.0 Hz, 1H), 7.43 – 7.27 (m, 4H), 7.25 – 7.20 (m, *J* = 10.3, 4.7 Hz, 2H), 6.97 – 6.91 (m, 3H), 5.77 (s, 1H), 3.60 (s, 3H). ¹³C NMR {¹H} (101 MHz, CDCl₃) δ 168.5, 163.6, 140.7, 140.7 (q, *J* = 38.3 Hz), 137.6, 134.3, 134.2, 133.0, 132.8, 130.7, 130.4, 129.5, 128.9, 128.8, 128.4, 127.7, 126.7, 125.9, 123.9, 121.6, 118.9 (q, *J* = 271.9 Hz), 111.0 (s), 75.6, 52.9, ¹⁹F NMR (376 MHz, CDCl₃) δ -61.93, HRMS (ESI-TOF) *m/z*: [M+H]⁺ calculated for C₂₄H₁₈F₃N₂O₄: 455.1213 found: 455.1230, [α]_D²² = +130.0° (c = 0.24 CHCl₃).

(P)-(1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (P)-56: **(P)-1**-Carboxyphenyl(2-trifluoromethyl)benzimidazole **(P)-1** (40 mg, 0.13 mmol, 1 eq) and **(1R,2S,5R)-(-)**-Menthol (20 mg, 0.13 mmol, 1 eq) purified via column chromatography (hexane: ethyl acetate 30:1, column dimensions: 1x10 cm). 49 mg of a white foamy solid (86 %). ¹H NMR (500 MHz, CDCl₃) δ 8.15 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.87 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.69 (ddd, *J* = 7.6, 7.5, 1.7 Hz, 1H), 7.64 (ddd, *J* = 7.6, 7.5, 1.4 Hz, 1H), 7.42 (d, *J* = 7.5 Hz, 1H), 7.32 (ddd, *J* = 8.1, 7.3, 1.2 Hz, 1H), 7.26 (td, *J* = 8.1, 7.3, 1.1 Hz, 1H), 6.89 (dt, *J* = 8.1, 1.0 Hz, 1H), 4.45 (ddd, *J* = 10.8, 10.8, 4.5 Hz, 1H), 1.46 (m, 1H), 1.42 (m, 1H), 1.40 (m, 1H), 1.09 (m, 1H), 1.01 (m, 1H), 0.76 (m, 1H), 0.74 (m, 1H), 0.72 (d, *J* = 7.0 Hz, 3H), 0.55 (d, *J* = 6.5 Hz, 3H), 0.50 (d, *J* = 7.0 Hz, 3H), -0.54 (q, *J* = 12.0, 12.0, 11.2 Hz, 1H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 141.1 (q, *J* = 38.4 Hz), 140.8, 138.0, 133.3, 132.6, 130.5, 130.2, 129.9, 125.9, 123.9, 121.5, 118.9 (q, *J* = 272.0 Hz), 110.9, 75.7, 46.3, 39.0, 33.8, 31., 24.6, 22.7, 21.8, 20.7, 15.7 ¹⁹F NMR (376 MHz, CDCl₃) δ -61.74 HRMS (ESI) *m/z*: [M+H]⁺ calculated for C₂₅H₂₈O₂N₂F₃: 445.2097.1057 found: 445.2099, [α]_D²² = -133.68° (c = 0.19 MeOH).

(M)-(1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (M)-57: **(M)-1**-Carboxyphenyl(2-trifluoromethyl)benzimidazole **(M)-1** (40 mg, 0.13 mmol, 1 eq) and **(1R,2S,5R)-(-)**-Menthol (20 mg, 0.13 mmol, 1 eq) purified via column chromatography (hexane: ethyl acetate 30:1, column dimensions: 1x10 cm). 48 mg of a white foamy solid (85 %). ¹H NMR (500 MHz, CDCl₃) δ 8.24 (dd, *J* = 7.5, 1.9 Hz, 1H), 7.89 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.69 (ddd, *J* = 7.6, 7.5, 1.7 Hz, 1H), 7.65 (ddd, *J* = 7.6, 7.5, 1.4 Hz, 1H), 7.38 (d, *J* = 7.6 Hz, 1H), 7.33 (ddd, *J* = 7.9, 7.3, 1.2 Hz, 1H), 7.38 (ddd, *J* = 8.2, 7.3, 1.3 Hz, 1H), 6.93 (dt, *J* = 8.2, 1.0 Hz, 1H), 4.55 (ddd, *J* = 11.0, 11.0, 4.4 Hz, 1H), 1.66 (m, 1H), 1.45 (m, 1H), 1.34 (m, 1H), 1.23 (m, 1H), 0.82 (m, 1H), 0.75 (m, 1H), 0.75 (d, *J* = 6.5 Hz, 3H), 0.70 (m, 1H), 0.58 (m, 1H), 0.40 (d, *J* = 7.0 Hz, 3H), 0.36 (d, *J* = 7.0 Hz, 3H), 0.32 (m, 1H), ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 164.0, 141.0 (q, *J* = 38.3 Hz), 140.7, 138.0, 133.7, 133.4, 133.0, 130.7, 130.2, 130.1, 125.9, 124.0, 121.5, 119.0 (q, *J* = 272.0 Hz), 111.1, 75.8, 46.3, 40.1, 34.0, 31.4, 25.5, 22.7, 21.9, 20.8, 15.5. ¹⁹F NMR (376 MHz, CDCl₃) δ -61.38 HRMS (ESI) *m/z*: [M+H]⁺ calculated for C₂₅H₂₈O₂N₂F₃: 445.2097.1057 found: 445.2101, [α]_D²² = -3.29° (c = 0.15 MeOH).

(P)-(1S,2R,4S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (P)-57 Using general procedure, from 15 mg of **(P)-1** and (-)-Borneol, 17 mg of oil (77 %). Purified by column chromatography (hexane: ethyl acetate 8.5:1, column dimensions 1x10 cm). ¹H NMR (400 MHz, CDCl₃) δ 8.22 – 8.19 (m, 1H), 7.97 – 7.92 (m, 1H), 7.72 (dq, *J* = 14.8, 7.5, 1.7 Hz, 2H), 7.42 (dd, *J* = 9.5, 1.4 Hz, 1H), 7.42 – 7.33 (m, 2H), 7.04 – 7.01 (m, 1H), 4.84 (ddd, *J* = 10.0, 3.6, 2.2 Hz, 1H), 2.07 – 1.97 (m, 1H), 1.53 (tdd, *J* = 12.0, 8.0, 4.4 Hz, 1H), 1.46 (t, *J* = 4.5 Hz, 1H), 1.17 (ddd, *J* = 13.8, 9.5, 4.6 Hz, 1H), 1.09 – 1.00 (m, 1H), 0.76 (s, *J* = 4.4 Hz, 3H), 0.75 (s, 3H), 0.74 – 0.67 (m, 1H), 0.64 (s, 3H), 0.24 (dd, *J* = 13.9, 3.6 Hz, 1H). ¹³C NMR{¹H} (101 MHz, CDCl₃) δ 165.3, 140.8 (q, *J* = 38.6 Hz), 140.8, 137.7, 133.4, 133.3, 132.5, 130.6, 130.1, 130.0, 126.1, 124.1, 121.7, 119.0 (q, *J* = 272.0 Hz), 110.9, 82.2, 48.7, 47.9, 44.6, 35.8, 27.8, 26.9, 19.7, 18.8, 13.4, ¹⁹F NMR (376 MHz, CDCl₃) δ = -61.65, HRMS (ESI) *m/z*: [M+H]⁺ calculated for C₂₅H₂₆F₃N₂O₂: 443.1946 found: 443.1941, [α]_D²² = -142.5° (c = 0.08 CHCl₃).

(M)-(1S,2R,4S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (M)-57 Using general procedure, from 15 mg of (M)-1 and (-)-Borneol, 15 mg of oil (68 %). Purified by column chromatography (hexane: ethyl acetate 8.5:1, column dimensions 1x10 cm). ¹H NMR (400 MHz, CDCl₃) δ 8.24 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.96 – 7.92 (m, 1H), 7.73 (pd, *J* = 7.5, 1.6 Hz, 2H), 7.44 – 7.33 (m, 3H), 7.08 – 7.02 (m, 1H), 4.95 – 4.90 (m, 1H), 2.14 (ddt, *J* = 14.0, 10.0, 4.0 Hz, 1H), 1.56 – 1.47 (m, 2H), 1.06 – 0.84 (m, 2H), 0.78 (s, *J* = 17.4 Hz, 3H), 0.73 (s, 3H) overlaps with 0.75– 0.70 (m, 1H), 0.57 (dd, *J* = 13.8, 3.6 Hz, 1H), 0.50 (s, 3H). ¹³C NMR {¹H} (101 MHz, CDCl₃) δ 165.0, 140.9 (q, *J* = 38.3 Hz), 140.8, 137.7, 133.5, 133.4, 132.6, 130.6, 130.1, 126.1, 124.1, 121.7, 119.0 (q, *J* = 271.9 Hz), 111.1, 81.8, 48.9, 48.00, 44.7, 36.1, 27.9, 26.8, 19.7, 18.8, 13.2, ¹⁹F NMR (376 MHz, CDCl₃) δ (ppm) = -61.90, HRMS (ESI) *m/z*: [M+H]⁺ calculated for C₂₅H₂₆F₃N₂O₂: 443.1946 found: 443.1942, [α]_D²² = -3.33° (c= 0.09 CHCl₃).

(P)-(3S,8S,9S,10R,13R,14S,17R)-10,13-Dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14, 15,16,17-tetradecahydro-1H-cyclopenta[*a*]phenanthren-3-yl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (P)-58

(P)-1-Carboxyphenyl(2-trifluoromethyl)benzimidazole (P)-1 (40 mg, 0.13 mmol, 1 eq) and cholesterol (50 mg, 0.13 mmol, 1 eq) purified via column chromatography (hexane: ethyl acetate 9:1, column dimensions: 1x10 cm). 64 mg of white foamy solid (72 %). ¹H NMR (500MHz, CDCl₃): δ 8.20 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.88 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.69 (ddd, *J* = 7.6, 7.5, 1.8 Hz, 1H), 7.64 (ddd, *J* = 7.6, 7.5, 1.5 Hz, 1H), 7.44 (d, *J* = 7.5 Hz, 1H), 7.33 (ddd, *J* = 7.8, 7.5, 1.1 Hz, 1H), 7.28 (td, *J* = 7.8, 7.5, 1.1 Hz, 1H), 6.91 (dd, *J* = 7.8, 1.3 Hz, 1H), 5.04 (m, 1H), 4.34 (dddd, *J* = 10.8, 10.8, 4.5 Hz, 1H), 0.50 (d, *J* = 7.0 Hz, 3H), 0.50 (d, *J* = 7.0 Hz, 3H), 0.50 (d, *J* = 7.0 Hz, 3H), 0.69 (s, 3H), 0.59 (s, 3H), 0.70 - 1.92 (overlapping multiplets) ¹³C{¹H} NMR, 126MHz, CDCl₃: δ 163.9, 141.2 (q, *J* = 38.5), 140.6, 139.3, 138.1, 133.6, 133.6, 132.9, 130.7, 130.1, 130.0, 126.0, 124.0, 122.6, 121.4, 119.0 (q, *J* = 272.2), 111.0, 75.3, 56.7, 56.2, 50.0, 42.4, 39.8, 39.6, 36.7, 36.6, 36.5, 36.3, 35.9, 31.9, 31.8, 28.3, 29.1, 26.9, 24.4, 23.9, 23.0, 22.7, 21.0, 19.2, 18.8, 11.9 ¹⁹F NMR (376 MHz, CDCl₃) δ -61.98 HRMS (ESI) *m/z*: [M+H]⁺ calculated for C₄₂H₅₄O₂N₂F₃: 675.4132, found: 675.4137 [α]_D²² = -96.41° (c= 0.64 CHCl₃).

(M)-(3S,8S,9S,10R,13R,14S,17R)-10,13-Dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14, 15,16,17-tetradecahydro-1H-cyclopenta[*a*]phenanthren-3-yl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (M)-58

(M)-1-Carboxyphenyl(2-trifluoromethyl)benzimidazole (M)-1 (40 mg, 0.13 mmol, 1 eq) and cholesterol (50 mg, 0.13 mmol, 1 eq) purified via column chromatography (hexane: ethyl acetate 9:1, column dimensions: 1x10 cm). 57 mg of a white foamy solid (64 %). ¹H NMR (500MHz, CDCl₃): δ 8.19 (dd, *J* = 7.6, 1.9 Hz, 1H), 7.88 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.69 (ddd, *J* = 7.6, 7.5, 1.7 Hz, 1H), 7.64 (ddd, *J* = 7.6, 7.5, 1.4 Hz, 1H), 7.43 (d, *J* = 7.5 Hz, 1H), 7.33 (ddd, *J* = 7.8, 7.4, 1.2 Hz, 1H), 7.28 (ddd, *J* = 7.6, 7.4, 1.3 Hz, 1H), 6.91 (dt, *J* = 7.6, 1.0 Hz, 1H), 5.17 (ddd, *J* = 11.0, 11.0, 4.4 Hz, 1H), ¹³C{¹H} NMR (126MHz, CDCl₃): δ 163.9, 141.2 (q, *J* = 38.4), 140.7, 139.2, 138.1, 133.6, 133.5, 132.8, 130.7, 130.1, 130.1, 126.0, 124.0, 123.0, 122.8, 121.5, 119.0 (q, *J* = 272.1), 111.0, 75.3, 56.8, 56.2, 50.0, 42.4, 39.8, 39.6, 37.2, 36.7, 36.5, 36.3, 35.9, 31.9, 31.8, 28.3, 28.1, 26.2, 25.7, 24.4, 23.9, 23.0, 22.7, 21.0, 19.3, 18.8, 12.0 ¹⁹F NMR (376 MHz, CDCl₃) δ -61.98 HRMS (ESI) *m/z*: [M+H]⁺ calculated for C₄₂H₅₄O₂N₂F₃: 675.4132, found: 675.4132 [α]_D²² = +69.83° (c= 0.57 CHCl₃).

(P)-Benzyl (1R,3aS,5aR,5bR,7aR,9S,11aR,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-9-((2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoyl)oxy)icosahydro-3aH-cyclopenta[*a*]chrysene-3a-carboxylate (P)-59

(P)-1-Carboxyphenyl(2-trifluoromethyl)benzimidazole (P)-1 (40 mg, 0.13 mmol, 1 eq) and benzyl betulinate (71 mg, 0.13 mmol, 1 eq) purified via column chromatography (hexane: ethyl acetate 12:1, column dimensions: 1x10 cm). 37 mg of a white foamy solid (35 %). ¹H NMR (500MHz, CDCl₃): δ 8.13 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.86 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.67 (ddd, *J* = 7.6, 7.5, 1.7 Hz, 1H), 7.62 (ddd, *J* = 7.6, 7.5, 1.4 Hz, 1H), 7.39 (d, *J* = 7.6 Hz, 1H), 7.32 (overlap, 1H), 7.29 (overlap, 1H), 7.21-7.30 (m, 5H), 6.96 (dt, *J* = 7.8, 1.3 Hz, 1H), 5.05 (d, 12.3 Hz, 1H), 5.00 (d, 12.3 Hz, 1H), 4.63 (d, 1.8

Hz, 1H), 4.51 (d, 1.8 Hz, 1H), 4.44 (dd, $J = 11.9, 4.6$ Hz, 1H), 2.92 (m, 1H), 2.16 (m, 1H), 2.05 (m, 1H), 1.68 (s, 3H), 0.81 (s, 3H), 0.62 (s, 3H), 0.58 (s, 3H), 0.52 (s, 3H), 0.11 (s, 3H), 0.70 - 1.92 (overlapping multiplets). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3): δ 175.9, 164.4, 150.6, 141.9 (q, $J = 38.6$), 140.8, 137.8, 136.60, 133.6, 133.2, 132.4, 130.6, 130.4, 130.0, 128.60 (2C), 128.4 (2C), 128.2, 125.8, 124.0, 121.5, 119.0 (q, $J = 272.1$), 111.2, 109.7, 82.7, 65.8, 56.6, 55.4, 50.4, 49.5, 47.0, 42.4, 40.7, 38.4, 38.2, 37.8, 37.0, 34.2, 32.2, 30.7, 29.8, 29.6, 27.7, 25.5, 23.3, 20.9, 19.4, 18.1, 16.1, 15.8 14.7 ^{19}F NMR (376 MHz, CDCl_3) δ -61.86 HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{52}\text{H}_{62}\text{O}_4\text{N}_2\text{F}_3$: 835.4656 found 835.4623 $[\alpha]_D^{22} = +4.05^\circ$ ($c = 0.37$ CHCl_3).

(M)-Benzyl (1R,3aS,5aR,5bR,7aR,9S,11aR,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-9-((2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoyl)oxy)icosahydro-3aH-cyclopenta[a]chrysene-3a-carboxylate (M)-59

(M)-1-Carboxyphenyl(2-trifluoromethyl)benzimidazole (M)-1 (40 mg, 0.13 mmol, 1 eq) and benzyl betulinate (71 mg, 0.13 mmol, 1 eq) purified via column chromatography (hexane: ethyl acetate 12:1, column dimensions: 1x10 cm). 67 mg of white foamy solid (62 %). ^1H NMR (500MHz, CDCl_3): δ 8.10 (dd, $J = 7.6, 1.7$ Hz, 1H), 7.86 (dd, $J = 8.0, 1.0$ Hz, 1H), 7.67 (ddd, $J = 7.6, 7.5, 1.4$ Hz, 1H), 7.62 (ddd, $J = 7.6, 7.5, 1.2$ Hz, 1H), 7.39 (d, $J = 7.5$ Hz, 1H), 7.31 (ddd, $J = 8.0, 7.5, 1.2$ Hz, 1H), 7.26 (overlap, 1H), 7.20-7.31 (m, 5H), 6.92 (dt, $J = 8.0, 1.0$ Hz, 1H), 4.63 (d, 1H), 5.06 (d, 12.2 Hz, 1H), 5.00 (d, 12.2 Hz, 1H), 4.63 (d, 1.8 Hz, 1H), 4.51 (d, 1.8 Hz, 1H), 4.33 (dd, $J = 11.0, 4.9$ Hz, 1H), 2.93 (m, 1H), 2.18 (m, 1H), 2.06 (m, 1H), 1.59 (s, 3H), 0.80 (s, 3H), 0.62 (s, 3H), 0.58 (s, 3H), 0.52 (s, 3H), 0.45 (s, 3H), 0.70 - 1.86 (overlapping multiplets). $^{13}\text{C}\{^1\text{H}\}$ NMR (126MHz, CDCl_3): δ 175.8, 164.7, 150.7, 140.84, 140.76 (q, $J = 38.5$), 137.6, 136.6, 133.4, 133.3, 132.3, 130.5, 130.1, 129.9, 128.6 (2C), 128.4 (2C), 128.5, 126.0, 124.0, 121.6, 119.0 (q, $J = 271.8$), 110.9, 109.8, 82.9, 65.8, 56.6, 55.4, 50.4, 49.5, 47.0, 42.4, 40.7, 38.4, 38.2, 37.7, 37.04, 37.00, 34.2, 32.2, 30.7, 29.8, 29.6, 27.9, 25.5, 22.5, 20.9, 19.5, 18.1, 16.3, 16.1, 15.9, 14.7 ^{19}F NMR (376 MHz, CDCl_3) δ -61.45 HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{52}\text{H}_{62}\text{O}_4\text{N}_2\text{F}_3$: 835.4656, found: 835.4619, $[\alpha]_D^{22} = +100.77^\circ$ ($c = 0.52$ CHCl_3).

(P)-(S)-2-Methylbutyl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (P)-60

Purified by CC (Hexane :EtOAc 8:1), Yield: 10 mg, (53%), clear oil ^1H NMR (400 MHz, CDCl_3) δ 8.27 – 8.22 (m, 1H), 7.96 – 7.92 (m, 1H), 7.73 (dtd, $J = 21.4, 7.6, 1.6$ Hz, 2H), 7.46 (dd, $J = 7.6, 1.4$ Hz, 1H), 7.37 (tdd, $J = 14.9, 7.2, 1.3$ Hz, 2H), 7.00 (ddd, $J = 7.7, 1.5, 0.8$ Hz, 1H), 3.77 (dd, $J = 10.8, 6.0$ Hz, 1H), 3.67 (dd, $J = 10.8, 6.9$ Hz, 1H), 1.20 (td, $J = 13.1, 6.8$ Hz, 1H), 1.11 – 0.99 (m, 1H), 0.92 – 0.80 (m, 1H), 0.72 (t, $J = 7.4$ Hz, 3H), 0.49 (d, $J = 6.7$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 164.7, 141.1 (q, $J = 39.4$ Hz), 140.9, 137.8, 133.9, 133.5, 132.7, 130.6, 130.1, 129.6, 126.0, 124.0, 121.6, 119.0 (q, $J = 271.8$ Hz), 110.9, 70.7, 33.8, 25.8, 15.9, 11.0. ^{19}F NMR (376 MHz, CDCl_3) δ -61.4. HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{20}\text{H}_{20}\text{F}_3\text{N}_2\text{O}_2$: 377.1471; found: 377.1470, $[\alpha]_D^{22} -47.14^\circ$ ($c = 0.10$, CHCl_3).

(M)-(S)-2-Methylbutyl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (M)-60

Purified by CC (Hexane: EtOAc 8:1), Yield: 14 mg (74%), clear oil ^1H NMR (400 MHz, CDCl_3) δ 8.26 – 8.22 (m, 1H), 7.96 – 7.92 (m, 1H), 7.76 (td, $J = 7.6, 1.8$ Hz, 1H), 7.70 (td, $J = 7.6, 1.5$ Hz, 1H), 7.46 (dd, $J = 7.6, 1.4$ Hz, 1H), 7.41 – 7.32 (m, 2H), 7.00 (ddd, $J = 7.7, 1.5, 0.8$ Hz, 1H), 3.71 (qd, $J = 10.8, 6.5$ Hz, 2H), 1.18 (dddd, $J = 13.3, 7.8, 6.6, 5.5$ Hz, 1H), 0.97 – 0.86 (m, 2H), 0.85 – 0.71 (m, 2H), 0.66 (t, $J = 7.3$ Hz, 3H), 0.60 (d, $J = 6.8$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 164.7, 141.1 (q, $J = 38.6$ Hz), 140.8, 137.8, 137.7, 133.9, 133.5, 132.7, 130.6, 130.1, 129.6, 126.0, 124.0, 121.6, 119.0 (q, $J = 272.0$ Hz), 110.9, 70.7, 33.7, 25.7, 16.0, 11.0. ^{19}F NMR (376 MHz, CDCl_3) δ -62.0. HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{20}\text{H}_{20}\text{F}_3\text{N}_2\text{O}_2$: 377.1471; found: 377.1470, $[\alpha]_D^{22} +57.00^\circ$ ($c = 0.14$, CHCl_3).

(P)-(R)-3-Bromo-2-methylpropyl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (P)-61

Purified by CC (Hexane: EtOAc 10:1) Yield: 13.3 mg (60%), clear oil $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.25 (ddd, $J = 7.8, 1.7, 0.5$ Hz, 1H), 7.96 – 7.93 (m, 1H), 7.78 (td, $J = 7.6, 1.8$ Hz, 1H), 7.72 (td, $J = 7.6, 1.4$ Hz, 1H), 7.48 (dd, $J = 7.7, 1.4$ Hz, 1H), 7.48 (dd, $J = 7.7, 1.4$ Hz, 1H), 7.43 – 7.34 (m, 2H), 7.00 (ddd, $J = 7.7, 1.5, 0.8$ Hz, 1H), 3.85 (dd, $J = 6.3, 0.8$ Hz, 2H), 2.96 (qd, $J = 10.3, 5.3$ Hz, 2H), 1.67 (dq, $J = 13.3, 6.7, 1.4$ Hz, 1H), 0.68 (d, $J = 6.8$ Hz, 3H). $^{13}\text{C NMR}\{^1\text{H}\}$ (101 MHz, CDCl_3) δ 164.4, 141.0 (q, $J = 38.5$ Hz), 140.8, 137.7, 133.9, 133.8, 132.8, 130.7, 130.2, 129.1, 126.2, 124.2, 121.7, 119.0 (q, $J = 271.5$ Hz), 110.8, 68.1, 36.3, 34.2, 15.4 $^{19}\text{F NMR}$ (376 MHz, CDCl_3) δ -61.9. **HRMS** (ESI- TOF) m/z : $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{19}\text{H}_{17}\text{BrF}_3\text{N}_2\text{O}_2$: 441.0420; found: 441.0422, $[\alpha]_d^{22} -70.77^\circ$ ($c = 0.13$, CHCl_3).

(M)-(R)-3-Bromo-2-methylpropyl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (M)-61

Purified by CC (Hexane: EtOAc 10:1) Yield: 10 mg (45%), clear oil $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.26 (dd, $J = 7.8, 1.6$ Hz, 1H), 7.97 – 7.93 (m, 5H), 7.79 (td, $J = 7.6, 1.8$ Hz, 1H), 7.73 (td, $J = 7.6, 1.4$ Hz, 1H), 7.49 (dd, $J = 7.7, 1.3$ Hz, 1H), 7.40 (pd, $J = 7.2, 1.4$ Hz, 1H), 7.05 – 6.99 (m, 1H), 3.89 (dd, $J = 11.1, 7.6$ Hz, 1H), 3.81 (dd, $J = 11.1, 5.2$ Hz, 1H), 2.83 (dd, $J = 10.3, 4.8$ Hz, 1H), 2.63 (dd, $J = 10.3, 5.1$ Hz, 1H), 1.55 (dtdd, $J = 11.9, 6.8, 5.1, 1.7$ Hz, 1H), 0.76 (d, $J = 6.8$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 164.4, 141.1 (d, $J = 40.0$ Hz), 140.7, 137.7, 133.9, 133.8, 132.9, 130.8, 130.1, 129.2, 126.2, 124.3, 121.7, 119.0 (q, $J = 271.9$ Hz), 110.9, 67.9, 36.4, 33.9, 15.4. $^{19}\text{F NMR}$ (471 MHz, CDCl_3) δ -62.0. **HRMS** (ESI- TOF) m/z : $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{19}\text{H}_{17}\text{BrF}_3\text{N}_2\text{O}_2$: 441.0420; found: 441.0421, $[\alpha]_d^{22} +25^\circ$ ($c = 0.1$, CHCl_3).

(P)-(R)-3-Methoxy-2-methyl-3-oxopropyl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (P)-62

Purified by CC (Hexane: EtOAc 4:1) Yield: 11.2 mg (55%), white foam $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.23 – 8.19 (m, 1H), 7.95 (ddd, $J = 8.1, 1.3, 0.8$ Hz, 1H), 7.77 (td, $J = 7.6, 1.7$ Hz, 1H), 7.70 (td, $J = 7.7, 1.4$ Hz, 1H), 7.48 (dd, $J = 7.7, 1.3$ Hz, 1H), 7.40 (ddd, $J = 8.1, 7.2, 1.4$ Hz, 1H), 7.35 (td, $J = 7.7, 7.2, 1.4$ Hz, 1H), 4.14 (dd, $J = 11.0, 7.2$ Hz, 1H), 3.86 (dd, $J = 11.0, 6.1$ Hz, 1H), 3.63 (s, 3H), 2.27 (td, $J = 7.2, 6.1$ Hz, 1H), 0.83 (d, $J = 7.2$ Hz, 3H). $^{13}\text{C NMR}\{^1\text{H}\}$ (101 MHz, CDCl_3) δ 173.8, 164.1, 141.1 (q, $J = 39.0$ Hz) 140.8, 137.7, 134.0, 133.8, 132.7, 130.7, 130.1, 129.0, 126.1, 124.1, 121.6, 118.9 (q, $J = 272.1$ Hz) 110.8, 66.7, 52.0, 38.5, 13.7. $^{19}\text{F NMR}$ (471 MHz, CDCl_3) δ -62.1. **HRMS** (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{20}\text{H}_{18}\text{F}_3\text{N}_2\text{O}_4$: 407.1213; found: 407.1212, $[\alpha]_d^{22} -70.0^\circ$ ($c = 0.11$, CHCl_3).

(M)-(R)-3-Methoxy-2-methyl-3-oxopropyl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (M)-62

Purified by CC (Hexane: EtOAc 4:1) Yield: 10 mg (50%), white foam $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.23 – 8.20 (m, 1H), 7.96 – 7.93 (m, 1H), 7.77 (td, $J = 7.6, 1.7$ Hz, 1H), 7.70 (td, $J = 7.7, 1.4$ Hz, 1H), 7.47 (dd, $J = 7.7, 1.3$ Hz, 1H), 7.40 (ddd, $J = 8.1, 7.2, 1.3$ Hz, 1H), 7.35 (td, $J = 7.7, 7.2, 1.3$ Hz, 1H), 6.97 (ddd, $J = 7.9, 1.3, 0.8$ Hz, 1H), 4.12 (dd, $J = 11.0, 7.2$ Hz, 1H), 3.96 (dd, $J = 11.0, 5.8$ Hz, 1H), 3.57 (s, 3H), 2.33 (td, $J = 7.2, 5.8$ Hz, 1H), 0.94 (d, $J = 7.2$ Hz, 3H). $^{13}\text{C NMR}\{^1\text{H}\}$ (101 MHz, CDCl_3) δ 173.7, 164.0, 141.0 (q, $J = 38.4$ Hz), 140.8, 137.7, 134.1, 133.8, 132.7, 130.7, 130.1, 129.0, 126.0, 124.0, 121.6, 119.0 (q, $J = 271.9$ Hz) 110.8, 66.6, 52.0, 38.5, 13.8. $^{19}\text{F NMR}$ (471 MHz, CDCl_3) δ -62.0. **HRMS** (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{20}\text{H}_{18}\text{F}_3\text{N}_2\text{O}_4$: 407.1213; found: 407.1214, $[\alpha]_d^{22} +49.0^\circ$ ($c = 0.10$, CHCl_3).

(P)-(S)-2-(Dimethylamino)-3-methylbutyl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (P)-63

Purified by HPLC, Yield: 8 mg (38%), clear oil $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.22 (dd, $J = 7.9, 1.5$ Hz, 1H), 7.96 (dt, $J = 8.2, 1.1$ Hz, 1H), 7.77 (td, $J = 7.6, 1.7$ Hz, 1H), 7.71 (td, $J = 7.7, 1.4$ Hz, 1H), 7.47 (dd, $J = 7.7, 1.3$ Hz, 1H), 7.40 (ddd, $J = 8.2, 7.2, 1.3$ Hz, 1H), 7.38 – 7.34 (m, 1H), 7.00 (ddd, $J = 8.0, 0.8$ Hz, 1H), 4.07 (dd, $J = 12.1, 5.5$ Hz, 1H), 4.01 (dd, $J = 12.1, 3.4$ Hz, 1H), 2.04 (s, 6H), 1.78 – 1.73 (m, 1H), 1.63 (dq, $J = 13.9, 6.8$ Hz, 1H), 0.87 (d, $J = 6.7$ Hz, 3H), 0.74 (d, $J = 6.7$ Hz, 3H). $^{13}\text{C NMR}\{^1\text{H}\}$

(126 MHz, CDCl₃) δ 164.3, 141.5, 141.2, 140.9, 140.9, 140.6, 137.8, 134.0, 133.6, 132.5, 130.7, 130.1, 129.4, 126.0, 124.1, 121.7, 119.0 (q, *J* = 272.0 Hz), 111.0, 68.2, 63.1, 41.6, 31.1, 28.2, 19.2. ¹⁹F NMR (376 MHz, CDCl₃) δ -61.9. HRMS (ESI) *m/z*: [M + H]⁺ calcd. for C₂₂H₂₅F₃N₃O₂: 420.1893; found: 420.1891, [α]_D²² -878.75° (c= 0.08, CHCl₃).

(M)-(S)-2-(Dimethylamino)-3-methylbutyl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (M)-63

Purified by HPLC, Yield: 5 mg (23%), clear oil ¹H NMR (500 MHz, CDCl₃) δ 8.23 – 8.21 (m, 1H), 7.97 – 7.94 (m, 1H), 7.77 (td, *J* = 7.6, 1.7 Hz, 1H), 7.71 (td, *J* = 7.7, 1.4 Hz, 1H), 7.48 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.40 (ddd, *J* = 8.2, 7.2, 1.3 Hz, 1H), 7.35 (ddd, *J* = 8.3, 7.2, 1.2 Hz, 1H), 7.00 (ddd, *J* = 8.0, 0.8 Hz, 1H), 4.03 (d, *J* = 4.5 Hz, 2H), 2.13 (s, 6H), 1.77 (br.s, 1H), 1.55 – 1.46 (m, 1H), 0.76 (d, *J* = 6.7 Hz, 3H), 0.61 (d, *J* = 6.7 Hz, 3H). ¹³C NMR{¹H} (126 MHz, CDCl₃) δ 164.4, 141.06 (app. d, *J* = 38.6 Hz), 140.9, 137.7, 134.0, 133.6, 132.5, 130.7, 130.1, 129.4, 126.0, 124.1, 121.7, 119.00 (app. d, *J* = 272.1 Hz), 110.9, 68.1, 63.2, 41.6, 31.1, 28.2, 20.6, 19.3. ¹⁹F NMR (376 MHz, CDCl₃) δ -61.9. HRMS (ESI) *m/z*: [M + H]⁺ calcd. for C₂₂H₂₅F₃N₃O₂: 420.1893; found: 420.1892, [α]_D²² -56.0° (c= 0.05, CHCl₃).

(P)-(2S)-3-((9-Methyl-3-oxa-9-azatricyclo[3.3.1.0^{2,4}]nonan-7-yl)oxy)-3-oxo-2-phenylpropyl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (P)-64

Following literature procedure:¹ Scopolamine hydrobromide trihydrate (80 mg, 0.18 mmol) was dissolved in DI water (5 mL) and 10% NaOH solution was added dropwise (4 drops) until pH of the solution was around 10. The solution was extracted 3× with diethyl ether. Organic layers were washed with brine, dried with MgSO₄ and evaporated to yield scopolamine freebase. Scopolamine freebase was then esterified according to general procedure.

Purified by CC (gradient Hexane: EtOAc 1:2 → EtOAc) Yield 12 mg (40%), light yellow oil ¹H NMR (500 MHz, CDCl₃) δ 8.13 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.96 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.76 (td, *J* = 7.7, 1.6 Hz, 1H), 7.68 (td, *J* = 7.7, 1.3 Hz, 1H), 7.46 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.41 (ddd, *J* = 8.2, 7.2, 1.2 Hz, 1H), 7.36 – 7.33 (m, 1H), 7.31 – 7.24 (m, 3H), 7.06 (dd, *J* = 7.6, 1.9 Hz, 2H), 6.95 (dt, *J* = 8.2, 0.9 Hz, 1H), 4.82 (t, *J* = 5.5 Hz, 1H), 4.48 (dd, *J* = 11.1, 8.7 Hz, 1H), 4.15 (dd, *J* = 11.1, 6.1 Hz, 1H), 3.31 (dd, *J* = 8.7, 6.1 Hz, 1H), 3.26 (d, *J* = 3.0 Hz, 1H), 3.08 (s, 1H), 2.90 (s, 1H), 2.48 (d, *J* = 3.0 Hz, 1H), 2.44 (s, 3H), 2.12 – 2.05 (m, 1H), 1.93 (dt, *J* = 14.8, 4.1 Hz, 1H), 1.52 (d, *J* = 15.1 Hz, 1H), 1.19 (d, *J* = 15.3 Hz, 1H). ¹³C NMR{¹H} (126 MHz, CDCl₃) δ 169.5, 163.9, 141.1 (app. d, *J* = 38.4 Hz), 140.8, 137.7, 134.9, 134.1, 133.9, 132.6, 130.7, 130.1, 129.2, 128.4, 127.9, 126.1, 124.0, 121.5, 118.95 (app. d, *J* = 272.1 Hz), 110.9, 67.1, 65.3, 58.0, 57.9, 56.4, 55.9, 50.3, 42.5, 31.1, 30.8. ¹⁹F NMR (471 MHz, CDCl₃) δ -61.94. HRMS (ESI) *m/z*: [M+H]⁺ calcd. for C₃₂H₂₉O₅N₃F₃: 592.2054 found: 592.2054.

(M)-(2S)-3-((9-Methyl-3-oxa-9-azatricyclo[3.3.1.0^{2,4}]nonan-7-yl)oxy)-3-oxo-2-phenylpropyl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (M)-64

Purified by CC (gradient Hexane: EtOAc 1:2 → EtOAc) Yield 10 mg (34%), light yellow oil ¹H NMR (500 MHz, CDCl₃) δ 8.16 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.98 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.77 (td, *J* = 7.7, 1.7 Hz, 1H), 7.69 (td, *J* = 7.7, 1.3 Hz, 1H), 7.48 (d, *J* = 7.7 Hz, 1H), 7.45 (ddd, *J* = 8.3, 7.2, 1.1 Hz, 1H), 7.37 (ddd, *J* = 8.2, 7.2, 1.1 Hz, 1H), 7.25 (d, *J* = 2.3 Hz, 3H), 6.96 (dt, *J* = 8.2, 1.0 Hz, 1H), 6.94 – 6.91 (m, 2H), 4.91 (t, *J* = 5.5 Hz, 1H), 4.56 (dd, *J* = 11.0, 9.4 Hz, 1H), 3.88 (dd, *J* = 11.1, 5.4 Hz, 1H), 3.40 (d, *J* = 2.9 Hz, 1H), 3.13 (s, 1H), 3.09 (dd, *J* = 9.4, 5.4 Hz, 1H), 2.90 (s, 1H), 2.46 (s, 1H), 2.45 (s, 3H), 2.11 (d, *J* = 15.4 Hz, 1H), 1.94 (d, *J* = 15.1 Hz, 1H), 1.69 (d, *J* = 15.0 Hz, 1H), 1.18 (d, *J* = 15.3 Hz, 1H). ¹³C NMR{¹H} (126 MHz, CDCl₃) δ 169.6, 164.0, 141.16 (app.d, *J* = 38.7 Hz), 140.8, 137.8, 137.8, 134.7, 134.0, 133.9, 132.7, 130.7, 130.1, 128.9, 128.3, 127.8, 126.2, 124.2, 121.5, 120.0 (q, *J* = 272.2 Hz) 110.9, 67.1, 65.4, 58.1, 57.9, 56.5, 55.9, 50.2, 42.3, 30.8, 30.7. ¹⁹F NMR (471 MHz, CDCl₃) δ -61.88. HRMS (ESI) *m/z*: [M+H]⁺ calcd. for C₃₂H₂₉O₅N₃F₃: 592.2054 found: 592.2055.

(P)-(S)-2-(6-Methoxynaphthalen-2-yl)propyl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (P)-65

Purified by CC (Hexane: EtOAc 6,5:1) Yield: 11 mg (44%), clear foam ¹H NMR (500 MHz, CDCl₃) δ 8.13 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.96 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.74 (td, *J* = 7.7, 1.6 Hz, 1H), 7.69 – 7.61 (m, 3H), 7.47 (dd, *J* = 7.7, 0.8 Hz, 1H), 7.44 – 7.35 (m, 2H), 7.31 (ddd, *J* = 8.2, 7.2, 1.1 Hz, 1H), 7.15 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.12 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.08 (d, *J* = 2.5 Hz, 1H), 6.96 (dt, *J* = 8.2, 0.9 Hz, 1H), 4.08 (dd, *J* = 10.8, 6.5 Hz, 1H), 3.99 (dd, *J* = 10.8, 8.1 Hz, 1H), 3.90 (s, 3H), 2.76 – 2.68 (m, 1H), 0.93 (d, *J* = 7.0 Hz, 3H). ¹³C NMR{¹H} (126 MHz, CDCl₃) δ 164.4, 157.6, 141.1 (q, *J* = 38.7 Hz), 140.9, 137.8, 134.0, 133.6, 132.6, 130.6, 130.0, 129.4, 129.3, 129.1, 127.1, 126.2, 126.0, 125.5, 124.1, 121.6, 119.0 (q, *J* = 271.9 Hz), 119.0, 110.9, 105.7, 70.7, 55.4, 38.6, 17.9. ¹⁹F NMR (471 MHz, CDCl₃) δ -61.96 HRMS (ESI) m/z: [M+H]⁺ calcd. for C₂₉H₂₄F₃O₃N₂: 505.1734; found: 505.1736 [α]_D²²: -75.46(c= 0.11 CHCl₃).

(M)-(S)-2-(6-Methoxynaphthalen-2-yl)propyl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (M)-65

Purified by CC (Hexane: EtOAc 6,5:1) Yield: 12 mg (50%), clear foam ¹H NMR (500 MHz, CDCl₃) δ 8.13 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.97 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.74 (td, *J* = 7.7, 1.6 Hz, 1H), 7.66 (td, *J* = 7.7, 1.3 Hz, 1H), 7.61 (t, *J* = 8.8 Hz, 2H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.41 (ddd, *J* = 8.3, 7.2, 1.1 Hz, 1H), 7.34 (ddd, *J* = 8.2, 7.2, 1.1 Hz, 1H), 7.30 (d, *J* = 1.1 Hz, 1H), 7.11 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.07 (d, *J* = 2.5 Hz, 1H), 7.05 (dd, *J* = 8.4, 1.8 Hz, 1H), 6.96 (dt, *J* = 8.2, 0.9 Hz, 1H), 4.09 (dd, *J* = 10.9, 6.5 Hz, 1H), 3.99 (dd, *J* = 10.9, 7.9 Hz, 1H), 3.90 (s, 3H), 2.73 – 2.61 (m, 1H), 1.08 (d, *J* = 7.0 Hz, 3H). ¹³C NMR{¹H} (126 MHz, CDCl₃) δ 164.4, 157.6, 141.2 (q, *J* = 38.4 Hz), 140.9, 137.8, 137.8, 134.0, 133.6, 132.6, 130.6, 130.0, 129.3, 129.2, 129.1, 127.1, 126.2, 126.1, 125.4, 124.1, 121.6, 119.0 (q, *J* = 272.1 Hz), 118.9, 110.9, 105.7, 70.7, 55.4, 38.5, 18.1. ¹⁹F NMR (471 MHz, CDCl₃) δ -61.93. HRMS (ESI) m/z: [M+H]⁺ calcd. for C₂₉H₂₄F₃O₃N₂: 505.1734; found: 505.1734 [α]_D²²: +61.88 (c= 0.12 CHCl₃).

(P)-(R)-Oxiran-2-ylmethyl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (P)-66 *

Purified by CC (Hexane: EtOAc 3:1) Yield: 7 mg (38%), clear oil ¹H NMR (500 MHz, CDCl₃) δ 8.27 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.96 – 7.93 (m, 1H), 7.80 (td, *J* = 7.7, 1.7 Hz, 1H), 7.73 (td, *J* = 7.7, 1.3 Hz, 1H), 7.52 (dd, *J* = 7.8, 0.8 Hz, 1H), 7.38 (dtd, *J* = 15.1, 7.2, 1.2 Hz, 2H), 6.98 (ddd, *J* = 7.9, 1.2, 0.7 Hz, 1H), 3.91 (qd, *J* = 12.0, 5.1 Hz, 2H), 2.71 (dtd, *J* = 6.0, 4.2, 2.5 Hz, 1H), 2.59 – 2.56 (m, 1H), 2.20 (dd, *J* = 4.8, 2.6 Hz, 1H). ¹³C NMR{¹H} (126 MHz, CDCl₃) δ 163.9, 140.9 (app. d, *J* = 38.2 Hz), 140.9, 137.8, 134.2, 134.0, 132.8, 130.7, 130.2, 128.8, 126.1, 124.1, 121.6, 119.0 (app. d, *J* = 272.4 Hz), 110.8, 66.4, 48.4, 44.8. ¹⁹F NMR (376 MHz, CDCl₃) δ -62.06. HRMS (ESI) m/z: [M+H]⁺ calcd. for C₁₈H₁₄F₃N₂O₃: 363.0957; found: 363.0950 [α]_D²²: -25,71° (c= 0.07 CHCl₃).

*S-alcohol was used. The priority of substituents changed after esterification.

(M)-(R)-Oxiran-2-ylmethyl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (M)-66 *

Purified by CC (Hexane: EtOAc 3:1) Yield: 6 mg (33%), clear oil ¹H NMR (500 MHz, CDCl₃) δ 8.31 – 8.24 (m, 1H), 7.94 (ddd, *J* = 8.1, 1.3, 0.8 Hz, 1H), 7.77 (dtd, *J* = 35.3, 7.6, 1.5 Hz, 2H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.44 – 7.33 (m, 2H), 7.00 (ddd, *J* = 7.8, 1.4, 0.8 Hz, 1H), 3.98 (dd, *J* = 12.0, 4.2 Hz, 1H), 3.88 (dd, *J* = 12.1, 5.8 Hz, 1H), 2.59 (tt, *J* = 4.8, 2.4 Hz, 1H), 2.56 (tdd, *J* = 5.9, 3.7, 2.1 Hz, 1H), 2.32 (dd, *J* = 4.8, 2.6 Hz, 1H). ¹³C NMR{¹H} (126 MHz, CDCl₃) δ 163.9, 141.1 (app. d, *J* = 38.2 Hz), 140.8, 137.8, 134.2, 134.0, 132.8, 130.8, 130.2, 128.8, 126.1, 124.1, 121.6, 119.00 (q, *J* = 271.8 Hz), 110.9, 66.4, 48.4, 44.8. ¹⁹F NMR (376 MHz, CDCl₃) δ -62.08. HRMS (ESI) m/z: [M+H]⁺ calcd. for C₁₈H₁₄F₃N₂O₃: 363.0957; found: 363.0950. [α]_D²²: +20,00° (c= 0.06 CHCl₃).

*S-alcohol was used. The priority of substituents changed after esterification.

(P)-(S)-(Tetrahydrofuran-2-yl)methyl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (P)-67

Purified by CC (Hexane: EtOAc 3,5:1) Yield: 15 mg (77%), clear oil ¹H NMR (400 MHz, CDCl₃) δ 8.26 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.98 – 7.91 (m, 1H), 7.73 (dtd, *J* = 25.4, 7.6, 1.5 Hz, 2H), 7.47 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.42 – 7.33 (m, 2H), 7.02 – 6.98 (m, 1H), 3.89 (d, *J* = 0.5 Hz, 1H), 3.87 (s, 1H), 3.72 – 3.65 (m, 1H), 3.61 – 3.54 (m, 1H), 3.48 (ddd, *J* = 12.4, 6.8, 5.7 Hz, 1H), 1.79 – 1.66 (m, 3H), 1.29 –

1.20 (m, 1H). $^{13}\text{C NMR}\{^1\text{H}\}$ (101 MHz, CDCl_3) δ 164.2, 141.1 (q, $J = 38.4$ Hz), 140.8, 137.8, 134.1, 133.7, 132.7, 130.6, 130.1, 129.2, 126.0, 124.0, 121.5, 119.0 (q, $J = 272.0$ Hz), 110.9, 75.8, 68.3, 67.4, 28.0, 25.5. $^{19}\text{F NMR}$ (376 MHz, CDCl_3) δ -62.0. **HRMS** (ESI) m/z : $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{20}\text{H}_{18}\text{F}_3\text{N}_2\text{O}_3$: 391.1270; found: 391.1264. $[\alpha]_D^{22}$: -68.46° ($c = 0.13$ CHCl_3).

(M)-(S)-(Tetrahydrofuran-2-yl)methyl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (M)-67

Purified by CC (Hexane: EtOAc 3,5:1) Yield 11 mg (56%), clear oil $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.26 (dd, $J = 7.7$, 1.8 Hz, 1H), 7.97 – 7.91 (m, 1H), 7.73 (dtd, $J = 25.6$, 7.6, 1.5 Hz, 2H), 7.47 (dd, $J = 7.7$, 1.3 Hz, 1H), 7.37 (dtd, $J = 15.0$, 7.2, 1.3 Hz, 2H), 7.02 – 6.96 (m, 1H), 3.88 (ddd, $J = 16.2$, 11.3, 5.6 Hz, 2H), 3.72 – 3.59 (m, 3H), 1.77 – 1.66 (m, 2H), 1.63 – 1.54 (m, 1H), 1.12 (ddd, $J = 15.6$, 12.4, 7.5 Hz, 1H). $^{13}\text{C NMR}\{^1\text{H}\}$ (101 MHz, CDCl_3) δ 164.2, 141.3 (app.d, $J = 38.6$ Hz), 140.9, 140.8, 137.7, 134.1, 133.7, 132.7, 130.6, 130.1, 129.1, 125.9, 124.0, 121.5, 119.0 (q, $J = 272.0$ Hz), 110.9, 75.9, 68.3, 67.3, 28.0, 25.5. $^{19}\text{F NMR}$ (376 MHz, CDCl_3) δ -62.04. **HRMS** (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd. For $\text{C}_{20}\text{H}_{18}\text{F}_3\text{N}_2\text{O}_3$: 391.1270; found: 391.1264 $[\alpha]_D^{22}$ +86.67° ($c = 0.12$ CHCl_3).

(P)-(S)-(5-Oxotetrahydrofuran-2-yl)methyl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (P)-68

Purified by CC (Hexane: EtOAc 2:1) Yield 9 mg (44%), clear oil $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.24 (dd, $J = 7.7$, 1.5 Hz, 1H), 7.97 – 7.92 (m, 1H), 7.81 (td, $J = 7.7$, 1.6 Hz, 1H), 7.73 (td, $J = 7.7$, 1.3 Hz, 1H), 7.51 (d, $J = 7.2$ Hz, 1H), 7.40 (pd, $J = 7.2$, 1.3 Hz, 1H), 7.01 (dd, $J = 7.0$, 1.5 Hz, 1H), 4.12 – 4.07 (m, 1H), 4.07 – 4.04 (m, 2H), 2.45 – 2.41 (m, 2H), 2.13 – 2.06 (m, 1H), 1.71 – 1.64 (m, 1H). $^{13}\text{C NMR}\{^1\text{H}\}$ (126 MHz, CDCl_3) δ 176.1, 163.7, 140.9 (q, $J = 38.4$ Hz) 140.7, 137.7, 134.2, 134.2, 132.7, 130.9, 130.3, 128.4, 126.3, 124.3, 121.5, 119.0 (q, $J = 272.0$ Hz) 111.0, 76.6, 66.1, 28.0, 23.9. $^{19}\text{F NMR}$ (376 MHz, CDCl_3) δ -61.97. **HRMS** (ESI) m/z : $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{20}\text{H}_{16}\text{F}_3\text{N}_2\text{O}_4$: 405.1057; found: 405.1056 $[\alpha]_D^{22}$: -62.50° ($c = 0.04$ CHCl_3).

(M)-(S)-(5-Oxotetrahydrofuran-2-yl)methyl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (M)-68

Purified by CC (Hexane: EtOAc 2:1) Yield 8.5 mg (42%), clear oil $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.26 – 8.23 (m, 1H), 7.97 – 7.94 (m, 1H), 7.81 (td, $J = 7.7$, 1.7 Hz, 1H), 7.73 (td, $J = 7.7$, 1.3 Hz, 1H), 7.51 (dd, $J = 7.8$, 1.2 Hz, 1H), 7.44 – 7.39 (m, 1H), 7.37 (td, $J = 7.7$, 7.2, 1.3 Hz, 1H), 7.00 (ddd, $J = 8.0$, 1.3, 0.8 Hz, 1H), 4.32 (tdd, $J = 7.4$, 5.8, 4.3 Hz, 1H), 4.10 (dd, $J = 12.0$, 4.3 Hz, 1H), 4.03 (dd, $J = 12.0$, 5.8 Hz, 1H), 1.93 (dddd, $J = 13.1$, 9.8, 7.3, 5.0 Hz, 1H), 1.47 – 1.40 (m, 1H). $^{13}\text{C NMR}\{^1\text{H}\}$ (126 MHz, CDCl_3) δ 176.0, 163.8, 141.20 (q, $J = 38.2$, 37.7 Hz), 140.8, 137.7, 134.2, 132.8, 130.8, 130.2, 128.4, 128.2, 126.2, 124.2, 121.7, 118.9 (q, $J = 272.2$ Hz), 110.8, 76.7, 65.9, 28.0, 23.9. $^{19}\text{F NMR}$ (376 MHz, CDCl_3) δ -62.04. **HRMS** (ESI) m/z : $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{20}\text{H}_{16}\text{F}_3\text{N}_2\text{O}_4$: 405.1057; found: 405.1055 $[\alpha]_D^{22}$: -153.0° ($c = 0.09$ CHCl_3).

(P)-((3aR,4R,6aR)-2,2-Dimethyl-6-oxotetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methyl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (P)-69

Purified by CC (Hexane: EtOAc 3:1) Yield: 21 mg (88%), clear oil $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.04 (ddd, $J = 7.8$, 1.6, 0.3 Hz, 1H), 7.97 – 7.94 (m, 1H), 7.83 (td, $J = 7.7$, 1.6 Hz, 1H), 7.74 (td, $J = 7.7$, 1.3 Hz, 1H), 7.44 – 7.37 (m, 2H), 7.01 – 6.98 (m, 1H), 4.63 (d, $J = 5.7$ Hz, 1H), 4.56 (t, $J = 3.2$ Hz, 1H), 4.45 (dd, $J = 5.7$, 0.5 Hz, 1H), 4.23 – 4.16 (m, 2H), 1.46 (s, 3H), 1.37 (s, 3H). $^{13}\text{C NMR}\{^1\text{H}\}$ (126 MHz, CDCl_3) δ 173.2, 163.0, 140.7, 140.6 (q, $J = 38.6$, 38.0 Hz), 137.7, 134.5, 134.5, 131.7, 131.1, 130.5, 127.9, 126.4, 124.3, 121.7, 119.0 (q, $J = 271.7$ Hz), 114.2, 110.8, 79.6, 75.0, 64.2, 26.8, 25.5. $^{19}\text{F NMR}$ (471 MHz, CDCl_3) δ -61.95. **HRMS** (ESI) m/z : $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{23}\text{H}_{20}\text{O}_6\text{N}_2\text{F}_3$: 477.1268 found: 477.1268 $[\alpha]_D^{22}$ -33.81° ($c = 0.21$ CHCl_3).

(M)-((3aR,4R,6aR)-2,2-Dimethyl-6-oxotetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methyl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (M)-69

Purified by CC (Hexane: EtOAc 3:1) Yield: 21 mg (88%), clear oil $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.12 (ddd, $J = 7.8$, 1.6, 0.4 Hz, 1H), 7.97 (ddd, $J = 8.1$, 1.4, 0.8 Hz, 1H), 7.83 (td, $J = 7.7$, 1.6 Hz, 1H), 7.74 (td, $J = 7.7$, 1.3 Hz, 1H), 7.53 (dd, $J = 7.8$, 1.2 Hz, 1H), 7.43 (ddd, $J = 8.0$, 7.2, 1.4 Hz, 1H), 7.41 – 7.37 (m, 1H), 6.99 (ddd, $J = 7.8$, 1.4, 0.8 Hz, 1H), 4.54 (t, $J = 3.5$ Hz, 1H), 4.34 (dd, $J = 12.4$, 3.7 Hz, 1H), 4.27 (d, $J = 5.7$ Hz, 1H), 4.11 – 4.08 (m, 1H), 4.08 – 4.07 (m, 1H), 1.41 (s, 3H), 1.30 (s, 3H). ^{13}C

NMR{¹H} (126 MHz, CDCl₃) δ 173.0, 163.2, 141.32 (q, *J* = 38.9 Hz), 140.9, 137.4, 134.5, 134.5, 134.3, 132.4, 131.0, 130.3, 127.8, 126.3, 124.4, 121.9, 118.88 (app.d *J* = 272.1 Hz), 114.1, 110.5, 79.7, 74.8, 64.0, 26.8, 25.7. **¹⁹F NMR** (471 MHz, CDCl₃) δ -62.10 **HRMS** (ESI) *m/z*: [M+H]⁺ calcd. for C₂₃H₂₀O₆N₂F₃: 477.1268 found: 477.1270 [α]_d²² +28.57° (c= 0.21 CHCl₃).

(P)-(S)-(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate* (P)-70

Purified by CC (Hexane: EtOAc 4:1) Yield: 9 mg (42%), clear oil **¹H NMR** (500 MHz, CDCl₃) δ 8.26 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.96 – 7.93 (m, 1H), 7.80 – 7.76 (m, 1H), 7.72 (td, *J* = 7.7, 1.3 Hz, 1H), 7.50 – 7.47 (m, 1H), 7.40 (ddd, *J* = 8.2, 7.2, 1.3 Hz, 1H), 7.36 (td, *J* = 7.7, 7.2, 1.2 Hz, 1H), 3.88 (qd, *J* = 11.2, 5.9 Hz, 2H), 3.75 (dd, *J* = 8.6, 6.3 Hz, 1H), 3.61 (p, *J* = 6.0 Hz, 1H), 3.37 (dd, *J* = 8.6, 5.2 Hz, 1H), 1.29 (s, 3H), 1.23 (s, 3H). **¹³C NMR**{¹H} (126 MHz, CDCl₃) δ 164.1, 141.0 (q, *J* = 38.5 Hz), 140.8, 137.7, 134.0, 133.9, 132.8, 130.7, 130.2, 128.9, 126.1, 124.2, 121.6, 119.0 (q, *J* = 271.8 Hz) 110.9, 109.7, 72.8, 66.4, 66.0, 26.8, 25.2. **¹⁹F NMR** (376 MHz, CDCl₃) δ -62.0. **HRMS** (ESI- TOF) *m/z*: [M + H]⁺ calcd. for C₂₁H₂₀F₃N₂O₄: 421.1370; found: 421.1371, [α]_d²² -78.89° (c= 0.9, CHCl₃).

*R-alcohol was used. The priority of substituents changed after esterification.

(M)-(S)-(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate*(M)-70

Purified by CC (Hexane: EtOAc 4:1) Yield: 11 mg (50%), clear oil **¹H NMR** (500 MHz, CHCl₃) δ 8.28 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.95 (d, *J* = 8.1 Hz, 1H), 7.78 (td, *J* = 7.6, 1.7 Hz, 1H), 7.72 (td, *J* = 7.7, 1.3 Hz, 1H), 7.48 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.41 (ddd, *J* = 8.2, 7.2, 1.2 Hz, 1H), 7.36 (td, *J* = 7.8, 7.3, 1.2 Hz, 1H), 6.98 (dt, *J* = 8.0, 0.9 Hz, 1H), 3.94 (dd, *J* = 11.1, 5.4 Hz, 1H), 3.85 (dd, *J* = 11.1, 6.5 Hz, 1H), 3.72 (ddd, *J* = 11.7, 6.3, 5.4 Hz, 1H), 3.49 (dd, *J* = 8.7, 6.3 Hz, 1H), 3.06 (dd, *J* = 8.7, 5.2 Hz, 1H), 1.29 (s, 3H), 1.25 (s, 3H). **¹³C NMR**{¹H} (126 MHz, CDCl₃) δ 164.0, 141.1 (q, *J* = 38.7 Hz), 140.8, 137.7, 134.0, 134.0, 132.9, 130.7, 130.2, 128.9, 126.1, 124.2, 121.6, 119.0 (q, *J* = 271.9 Hz), 110.9, 109.7, 72.8, 66.3, 65.9, 26.9, 25.2. **¹⁹F NMR** (376 MHz, CDCl₃) δ -62.1. **HRMS** (ESI- TOF) *m/z*: [M + H]⁺ calcd. for C₂₁H₂₀F₃N₂O₄: 421.1370; found 421.1370, [α]_d²² +27.3° (c= 0.11, CHCl₃).

*R-alcohol was used. The priority of substituents changed after esterification.

(P)-((4R,5R)-5-(Hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (P)-71

Purified by CC (Hexane: EtOAc 2.5:1) Yield: 10 mg (44%), clear oil **¹H NMR** (500 MHz, CDCl₃) δ 8.24 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.75 (dtd, *J* = 36.6, 7.7, 1.4 Hz, 2H), 7.51 (d, *J* = 7.5 Hz, 1H), 7.44 – 7.32 (m, 2H), 7.00 (d, *J* = 8.0 Hz, 1H), 4.13 (dd, *J* = 11.9, 3.6 Hz, 1H), 3.93 (dd, *J* = 11.9, 5.7 Hz, 1H), 3.71 (ddd, *J* = 7.9, 5.7, 3.6 Hz, 1H), 3.67 – 3.60 (m, 2H), 3.52 – 3.44 (m, 1H), 1.33 (s, 3H), 1.30 (s, 3H). **¹³C NMR**{¹H} (126 MHz, CDCl₃) δ 164.0, 141.1 (app. d, *J* = 38.3 Hz), 140.8, 137.7, 134.2, 134.0, 132.5, 130.7, 130.2, 128.8, 126.1, 124.1, 119.0 (app. d, *J* = 272.0 Hz), 110.9, 109.9, 78.1, 74.9, 65.3, 62.0, 31.1, 27.1, 27.0. **¹⁹F NMR** (376 MHz, CDCl₃) δ -61.9. **HRMS** (ESI) *m/z*: [M+H]⁺ calcd. for C₂₂H₂₂F₃N₂O₅: 451.1481; found: 451.1475 [α]_d²²: -46,00° (c= 0.09 CHCl₃).

(M)-((4R,5R)-5-(Hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (M)-71

Purified by CC (Hexane: EtOAc 2.5:1) Yield: 12 mg (53%), clear oil **¹H NMR** (500 MHz, CDCl₃) δ 8.24 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.79 (td, *J* = 7.6, 1.0 Hz, 1H), 7.72 (t, *J* = 7.7 Hz, 1H), 7.50 (d, *J* = 7.7 Hz, 1H), 7.38 (dt, *J* = 15.0, 7.2 Hz, 2H), 6.99 (d, *J* = 8.1 Hz, 1H), 4.13 (dd, *J* = 11.9, 3.5 Hz, 1H), 3.97 (dd, *J* = 11.9, 5.5 Hz, 1H), 3.76 – 3.67 (m, 1H), 3.58 – 3.50 (m, 1H), 3.46 – 3.37 (m, 2H), 1.35 (s, 3H), 1.26 (s, 3H). **¹³C NMR**{¹H} (126 MHz, CDCl₃) δ 164.0, 141.2 (app. d, *J* = 38.0 Hz), 140.9, 137.7, 134.2, 134.0, 132.6, 130.7, 130.2, 128.8, 126.1, 124.1, 121.6, 118.9 (app. d, *J* = 271.6 Hz), 110.8, 109.8, 77.9, 74.9, 65.0, 61.9, 29.8, 27.0. **¹⁹F NMR** (376 MHz, CDCl₃) δ -62.05. **HRMS** (ESI) *m/z*: [M+H]⁺ calcd. for C₂₂H₂₂F₃N₂O₅: 451.1481; found: 451.1475 [α]_d²²: +33,63° (c= 0.11 CHCl₃).

(P)-tert-Butyl (S)-2-(((2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoyl)oxy)methyl)pyrrolidine-1-carboxylate (P)-72

Purified by CC (Hexane: EtOAc 4:1) Yield: 8 mg (30%), clear oil ¹H NMR (500 MHz, CDCl₃) δ 8.25 (d, *J* = 7.4 Hz, 1H), 7.94 (d, *J* = 8.2 Hz, 1H), 7.81 – 7.68 (m, 2H), 7.48 (d, *J* = 7.1 Hz, 1H), 7.42 – 7.38 (m, 1H), 7.35 (td, *J* = 7.7, 7.3, 1.2 Hz, 1H), 6.99 (d, *J* = 8.0 Hz, 1H), 4.15 – 3.97 (m, 1H), 3.83 – 3.64 (m, 1H), 3.20 (d, *J* = 23.9 Hz, 3H), 1.75 – 1.59 (m, 4H), 1.40 (s, 3H), 1.34 (s, 6H). ¹³C NMR{¹H} (126 MHz, CDCl₃) δ 164.2, 154.3, 141.27 (d, *J* = 38.7 Hz), 140.8, 137.7, 133.9, 133.8, 132.8, 130.7, 130.2, 129.1, 126.1, 124.1, 121.6, 119.0 (q, *J* = 272.1 Hz), 110.8, 79.9, 65.7, 55.1, 46.4, 29.8, 28.5, 22.7. ¹⁹F NMR (471 MHz, CDCl₃) δ -61.3. HRMS (ESI) *m/z*: [M+H]⁺ calcd. for C₂₅H₂₇F₃N₃O₄: 490.1948; found: 490.1950 [α]_D²²: -913.7° (c= 0.08 CHCl₃).

(M)-tert-Butyl (S)-2-(((2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoyl)oxy)methyl)pyrrolidine-1-carboxylate (M)-72

Purified by CC (Hexane: EtOAc 4:1) Yield: 14 mg (58%), clear oil ¹H NMR (500 MHz, CDCl₃) δ 8.25 (d, *J* = 7.4 Hz, 1H), 7.94 (d, *J* = 8.2 Hz, 1H), 7.81 – 7.68 (m, 2H), 7.48 (d, *J* = 7.1 Hz, 1H), 7.42 – 7.38 (m, 1H), 7.35 (td, *J* = 7.7, 7.3, 1.2 Hz, 1H), 6.99 (d, *J* = 8.0 Hz, 1H), 4.15 – 3.97 (m, 1H), 3.83 – 3.64 (m, 1H), 3.20 (d, *J* = 23.9 Hz, 3H), 1.75 – 1.59 (m, 4H), 1.40 (s, 3H), 1.34 (s, 6H). ¹³C NMR{¹H} (126 MHz, CDCl₃) δ 164.2, 154.3, 141.27 (d, *J* = 38.7 Hz), 140.8, 137.7, 133.9, 133.8, 132.8, 130.7, 130.2, 129.1, 126.1, 124.1, 121.6, 118.99 (q, *J* = 272.1 Hz), 110.8, 79.9, 65.7, 55.1, 46.4, 29.8, 28.5, 22.7. ¹⁹F NMR (471 MHz, CDCl₃) δ -61.3. HRMS (ESI) *m/z*: [M+H]⁺ calcd. for C₂₅H₂₇F₃N₃O₄: 490.1948; found: 490.1949 [α]_D²²: -32.86° (c= 0.14 CHCl₃).

(P)-((2S,5R)-1-Methyl-5-phenylpyrrolidin-2-yl)methyl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (P)-73

Purified by CC (Hexane: EtOAc 6:1) Yield: 15 mg (62%), clear foam ¹H NMR (400 MHz, CDCl₃) δ 8.30 – 8.24 (m, 1H), 7.99 – 7.94 (m, 1H), 7.75 (dtd, *J* = 23.0, 7.6, 1.6 Hz, 2H), 7.51 – 7.47 (m, 1H), 7.37 (dtd, *J* = 9.2, 7.2, 1.2 Hz, 2H), 7.29 – 7.23 (m, 4H), 7.22 – 7.17 (m, 1H), 7.01 (ddd, *J* = 8.0, 1.3, 0.8 Hz, 1H), 3.88 (ddd, *J* = 18.2, 10.8, 5.9 Hz, 2H), 3.21 (dd, *J* = 9.8, 6.3 Hz, 1H), 2.15 – 2.07 (m, 1H), 1.94 (s, 3H), 1.98 – 1.89 (m, 4H), 1.67 (ddd, *J* = 17.2, 12.6, 8.7 Hz, 1H), 1.53 (ddd, *J* = 18.8, 12.1, 9.3 Hz, 1H), 1.34 – 1.27 (m, 1H). ¹³C NMR{¹H} (126 MHz, CDCl₃) δ 164.5, 143.4, 141.1 (q, *J* = 38.4 Hz), 140.9, 137.8, 134.0, 133.6, 132.7, 130.7, 130.1, 129.5, 128.4, 127.3, 127.1, 126.1, 124.1, 121.6, 119.0 (q, *J* = 271.9 Hz), 110.9, 72.1, 68.6, 63.6, 39.5, 34.4, 27.5. ¹⁹F NMR (376 MHz, CDCl₃) δ -61.92. HRMS (ESI) *m/z*: [M+H]⁺ calcd. for: C₂₇H₂₅F₃N₃O₂: 480.1899 found: 480.1891 [α]_D²²: -463.34 (c= 0.15 CHCl₃).

(M)-((2S,5R)-1-Methyl-5-phenylpyrrolidin-2-yl)methyl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (M)-73

Purified by CC (Hexane: EtOAc 6:1) Yield: 18 mg (75%), clear foam ¹H NMR (400 MHz, CDCl₃) δ 8.31 – 8.27 (m, 1H), 7.98 – 7.95 (m, 1H), 7.75 (dtd, *J* = 22.3, 7.5, 1.6 Hz, 2H), 7.48 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.38 (dddd, *J* = 21.8, 8.3, 7.2, 1.2 Hz, 2H), 7.29 – 7.17 (m, 6H), 3.94 (ddd, *J* = 18.1, 10.9, 5.7 Hz, 2H), 3.22 (dd, *J* = 9.3, 6.6 Hz, 1H), 2.33 – 2.22 (m, 1H), 2.08 (s, 3H), 1.92 – 1.80 (m, 1H), 1.48 – 1.33 (m, 2H), 1.09 – 0.98 (m, 1H). ¹³C NMR{¹H} (126 MHz, CDCl₃) δ 164.5, 143.5, 141.1 (q, *J* = 38.5 Hz), 140.9, 137.8, 134.0, 133.7, 132.8, 130.7, 130.11, 129.5, 128.4, 127.3, 127.1, 126.0, 124.1, 121.6, 119.0 (q, *J* = 272.1 Hz), 111.0, 72.0, 68.4, 63.8, 39.6, 34.3, 27.2. ¹⁹F NMR (376 MHz, CDCl₃) δ -61.98. HRMS (ESI) *m/z*: [M+H]⁺ calcd. for C₂₇H₂₅F₃N₃O₂: 480.1899 found: 480.1891 [α]_D²²: +61.88 (c= 0.16 CHCl₃).

(P)-(R)-(5-Oxopyrrolidin-2-yl)methyl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (P)-74

Purified by CC (EtOAc) Yield: 8 mg (40%), clear oil ¹H NMR (400 MHz, CDCl₃) δ 8.25 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.97 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.82 (td, *J* = 7.6, 1.7 Hz, 1H), 7.74 (td, *J* = 7.7, 1.4 Hz, 1H), 7.53 (dd, *J* = 7.8, 0.8 Hz, 1H), 7.46 – 7.41 (m, 1H), 7.39 (td, *J* = 7.7, 7.3, 1.2 Hz, 1H), 5.37 (s, 1H), 3.97 (dd, *J* = 11.3, 4.4 Hz, 1H), 3.66 (dd, *J* = 11.3, 7.4 Hz, 1H), 3.29 (ddd, *J* = 12.9, 7.7, 5.1 Hz, 1H), 2.14 (ddd, *J* = 9.1, 7.1, 3.2 Hz, 2H), 1.87 (dddd, *J* = 13.3, 9.1, 8.0, 6.7 Hz, 1H). ¹³C NMR{¹H} (101 MHz, CDCl₃) δ 177.5, 164.2, 141.2 (q, *J* = 38.2 Hz), 140.7, 137.8, 134.3, 133.9, 133.0, 130.9, 130.2, 128.5,

126.3, 124.4, 121.7, 118.9 (q, $J = 272.0$ Hz), 110.8, 68.2, 52.2, 29.1, 23.1. ^{19}F NMR (471 MHz, CDCl_3) δ -62.0. HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{20}\text{H}_{17}\text{F}_3\text{N}_3\text{O}_3$: 404.1217; found: 404.1216, $[\alpha]_d^{22}$ -63.75° ($c = 0.08$, CHCl_3).

(M)-(R)-(5-Oxopyrrolidin-2-yl)methyl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (M)-74

Purified by CC (EtOAc) Yield: 8 mg (40%), clear oil ^1H NMR (400 MHz, CDCl_3) δ 8.33 – 8.24 (m, 1H), 8.00 – 7.96 (m, 1H), 7.82 (td, $J = 7.6, 1.7$ Hz, 1H), 7.75 (td, $J = 7.7, 1.4$ Hz, 1H), 7.52 (dd, $J = 7.7, 1.3$ Hz, 1H), 7.51 – 7.43 (m, 2H), 7.06 – 7.02 (m, 1H), 4.42 (s, 1H), 3.86 (dd, $J = 11.2, 3.7$ Hz, 1H), 3.70 (dd, $J = 11.2, 8.8$ Hz, 1H), 3.11 – 3.03 (m, 1H), 2.18 – 2.13 (m, 2H), 2.02 (dq, $J = 13.1, 7.9$ Hz, 1H). ^{13}C NMR $\{^1\text{H}\}$ (101 MHz, CDCl_3) δ 177.2, 164.1, 141.3 (q, $J = 38.9$ Hz), 140.6, 137.8, 134.3, 133.7, 133.2, 131.0, 130.2, 128.6, 126.5, 124.7, 121.8, 118.9 (q, $J = 272.0$ Hz), 110.8, 68.8, 51.9, 29.0, 22.9. ^{19}F NMR (471 MHz, CDCl_3) δ -62.2. HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{20}\text{H}_{17}\text{F}_3\text{N}_3\text{O}_3$: 404.1217; found: 404.1217, $[\alpha]_d^{22}$ -77.50° ($c = 0.08$, CHCl_3).

(P)-((3aR,5R,5aS,8aS,8bR)-2,2,7,7-Tetramethyltetrahydro-5H-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)methyl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (P)-75

Purified by CC (Hexane: EtOAc 4:1) Yield 8 mg (30%), clear oil ^1H NMR (500 MHz, CDCl_3) δ 8.27 (dd, $J = 7.9, 1.6$ Hz, 1H), 7.93 (dt, $J = 8.2, 0.9$ Hz, 1H), 7.76 (td, $J = 7.6, 1.7$ Hz, 1H), 7.70 (td, $J = 7.7, 1.4$ Hz, 1H), 7.45 (dd, $J = 7.7, 1.1$ Hz, 1H), 7.37 (ddd, $J = 8.2, 7.2, 1.2$ Hz, 1H), 7.32 (ddd, $J = 8.2, 7.2, 1.2$ Hz, 1H), 6.98 – 6.96 (m, 1H), 5.43 (d, $J = 5.0$ Hz, 1H), 4.49 (dd, $J = 7.9, 2.5$ Hz, 1H), 4.24 (dd, $J = 5.0, 2.5$ Hz, 1H), 4.20 (dd, $J = 11.3, 6.1$ Hz, 1H), 4.03 (dd, $J = 11.2, 6.9$ Hz, 1H), 3.81 (dd, $J = 7.9, 1.9$ Hz, 1H), 3.64 (td, $J = 6.4, 1.8$ Hz, 1H), 1.37 (s, 3H), 1.34 (s, 3H), 1.29 (s, 6H). ^{13}C NMR $\{^1\text{H}\}$ (126 MHz, CDCl_3) δ 163.9, 141.11 (q, $J = 38.4$ Hz), 140.8, 137.7, 134.2, 133.7, 132.7, 130.7, 130.2, 128.9, 125.9, 124.0, 121.6, 119.0 (q, $J = 271.9$ Hz), 113.6, 110.8, 109.6, 108.8, 96.2, 70.6, 70.6, 70.5, 65.4, 64.1, 26.1, 26.0, 25.0, 24.5. ^{19}F NMR (376 MHz, CDCl_3) δ -61.9. HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd. For $\text{C}_{27}\text{H}_{28}\text{F}_3\text{N}_2\text{O}_7$: 549.1843; found: 549.1843, $[\alpha]_d^{22}$: -125.0° ($c = 0.08$ CHCl_3).

(M)-((3aR,5R,5aS,8aS,8bR)-2,2,7,7-Tetramethyltetrahydro-5H-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)methyl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (M)-75

Purified by CC (Hexane: EtOAc 4:1), Yield 8 mg (30%), clear oil ^1H NMR (500 MHz, CDCl_3) δ 8.32 – 8.30 (m, 1H), 7.97 – 7.94 (m, 1H), 7.77 (td, $J = 7.6, 1.7$ Hz, 1H), 7.71 (td, $J = 7.7, 1.4$ Hz, 1H), 7.47 (dd, $J = 7.7, 1.3$ Hz, 1H), 7.43 – 7.39 (m, 1H), 7.37 (ddd, $J = 8.3, 7.2, 1.3$ Hz, 1H), 7.02 (ddd, $J = 8.0, 1.2, 0.8$ Hz, 2H), 5.40 (d, $J = 5.0$ Hz, 1H), 4.28 (dd, $J = 7.9, 2.4$ Hz, 1H), 4.21 (dd, $J = 5.0, 2.4$ Hz, 1H), 4.10 (dd, $J = 11.0, 7.3$ Hz, 1H), 4.02 (dd, $J = 11.0, 6.3$ Hz, 1H), 3.53 – 3.49 (m, 1H), 2.86 (dd, $J = 7.9, 1.9$ Hz, 1H), 1.60 (s, 3H), 1.32 (s, 3H), 1.32 (s, 3H), 1.15 (s, 3H). ^{13}C NMR $\{^1\text{H}\}$ (126 MHz, CDCl_3) δ 163.9, 141.13 (q, $J = 38.5$ Hz), 140.8, 137.8, 134.0, 133.8, 133.1, 130.7, 130.1, 129.0, 125.9, 123.8, 122.0, 119.0 (q, $J = 272.6$ Hz), 111.0, 109.2, 109.0, 96.2, 70.6, 69.8, 65.0, 63.8, 26.2, 25.9, 25.1, 24.3. ^{19}F NMR (376 MHz, CDCl_3) δ -62.1. HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{27}\text{H}_{28}\text{F}_3\text{N}_2\text{O}_7$: 549.1843; found: 549.1845, $[\alpha]_d^{22}$: -832.5° ($c = 0.08$ CHCl_3).

(P)-tert-Butyl-(R)-2-((2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzamido)methyl)pyrrolidine-1-carboxylate (P)-76

TBBA (20 mg, 0.065 mmol, 1 eq.) was dissolved in dry DMF (1.5 mL). Amine (13mg, 0.065 mmol, 1 eq.) was added followed by HOBT·H₂O (20 mg, 0.13 mmol, 2 eq.) and EDCI (26 mg, 0.13 mmol, 2 eq.). Reaction was stirred at room temperature for 3 hrs. After 3 hrs. the solution was diluted with EtOAc (5 mL) and washed 3× with 10% HCl and 10% K₂CO₃ and once with brine. Organic layer was dried with MgSO₄ and purified by column chromatography (hexane: EtOAc 2:1) Yield 15mg (62%), clear oil ^1H NMR (500 MHz, CDCl_3) δ 7.91 (dd, $J = 6.9, 1.8$ Hz, 1H), 7.85 – 7.78 (m, 1H), 7.68 – 7.60 (m, 2H), 7.45 – 7.41 (m, 1H), 7.39 – 7.32 (m, 2H), 7.05 (dd, $J = 6.8, 1.8$ Hz, 1H), 3.76 (s, 1H), 3.32 (dt, $J = 10.8, 7.8$ Hz, 1H), 3.26 – 3.19 (m, 1H), 3.16 (dt, $J = 13.6, 4.3$ Hz, 1H), 3.04 (s, 1H), 1.84 – 1.77 (m, 3H), 1.75 – 1.69 (m, 2H), 1.46 (s, 9H). ^{13}C NMR $\{^1\text{H}\}$ (126 MHz, CDCl_3) δ 165.6, 156.8, 141.1 (q, $J = 38.3$ Hz), 140.6, 137.8, 134.9, 132.6, 131.5, 130.5, 129.7, 129.1, 125.8, 123.9, 121.5, 119.1 (q, $J = 272.1$ Hz),

111.4, 80.3, 56.2, 47.2, 46.7, 29.6, 28.5, 23.8. ^{19}F NMR (376 MHz, CDCl_3) δ -61.5. HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd. For $\text{C}_{25}\text{H}_{28}\text{O}_3\text{N}_4\text{F}_3$: 489.2108; found: 489.2111 $[\alpha]_d^{22}$ -8.67° ($c=0.15$ CHCl_3).

(M)-tert-Butyl-(R)-2-((2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzamido)methyl)pyrrolidine-1-carboxylate (M)-76

Following same procedure as for compound (P)-76.

Purified by CC (hexane: EtOAc 2:1) Yield 12 mg (50%), clear oil ^1H NMR (500 MHz, CDCl_3) δ 7.91 (dd, $J = 6.7, 2.0$ Hz, 1H), 7.83 – 7.77 (m, 1H), 7.67 – 7.60 (m, 2H), 7.45 – 7.41 (m, 1H), 7.35 (tt, $J = 7.2, 5.9$ Hz, 2H), 7.09 – 7.05 (m, 1H), 3.90 (s, 1H), 3.33 (dt, $J = 10.9, 7.8$ Hz, 1H), 3.27 (dt, $J = 11.0, 6.2$ Hz, 1H), 3.15 (s, 1H), 3.13 – 3.08 (m, 1H), 1.84 (s, 2H), 1.79 – 1.73 (s, 2H), 1.44 (s, 9H). ^{13}C NMR{ ^1H } (126 MHz, CDCl_3) δ 165.6, 157.0, 141.2 (q, $J = 38.0$ Hz) 140.6, 137.8, 135.0, 132.7, 131.5, 130.6, 129.9, 128.8, 125.8, 123.9, 121.5, 119.0 (q, $J = 272.3$ Hz) 111.4, 80.3, 56.2, 47.2, 46.6, 29.5, 28.5, 23.8. ^{19}F NMR (376 MHz, CDCl_3) δ -61.8. HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd. For $\text{C}_{25}\text{H}_{28}\text{O}_3\text{N}_4\text{F}_3$: 489.2108; found: 489.2112 $[\alpha]_d^{22}$ -14.17° ($c=0.12$ CHCl_3).

(P)-(S)-2-((tert-Butoxycarbonyl)amino)-2-phenylethyl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (P)-77

Purified by CC (hexane: EtOAc 5:1) Yield 15 mg (57%), amorphous solid ^1H NMR (400 MHz, CDCl_3) δ 8.19 (dd, $J = 7.8, 1.5$ Hz, 1H), 7.95 (d, $J = 7.8$ Hz, 1H), 7.77 (td, $J = 7.7, 1.7$ Hz, 1H), 7.69 (td, $J = 7.7, 1.3$ Hz, 1H), 7.51 – 7.46 (m, 1H), 7.43 – 7.37 (m, 1H), 7.37 – 7.32 (m, 1H), 7.30 – 7.23 (m, 3H), 7.12 – 7.08 (m, 2H), 6.98 – 6.93 (m, 1H), 4.75 (s, 2H), 4.29 – 4.21 (m, 1H), 4.08 (d, $J = 10.6$ Hz, 1H), 1.39 (s, 9H). ^{13}C NMR{ ^1H } (101 MHz, CDCl_3) δ 163.9, 155.2, 141.14 (q, $J = 38.6$ Hz), 140.8, 138.3, 137.6, 134.3, 133.9, 132.7, 130.7, 130.2, 128.8, 128.6, 128.0, 126.5, 126.1, 124.1, 121.6, 118.96 (q, $J = 272.2$ Hz), 110.8, 80.0, 67.3, 53.7, 28.4. ^{19}F NMR (376 MHz, CDCl_3) δ -62.01 HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd. For $\text{C}_{28}\text{H}_{27}\text{N}_3\text{O}_4\text{F}_3$; 526.1948; found: 526.1951 $[\alpha]_d^{22}$ +52.86° ($c=0.15$ CHCl_3). ^1H NMR (400 MHz, Acetone- D_6) δ 8.24 (dd, $J = 7.8, 1.6$ Hz, 1H), 7.94 (t, $J = 7.4$ Hz, 1H), 7.87 (dq, $J = 7.2, 3.6$ Hz, 1H), 7.82 (t, $J = 7.7$ Hz, 1H), 7.74 (d, $J = 7.8$ Hz, 1H), 7.41 (td, $J = 6.7, 6.0, 4.0$ Hz, 2H), 7.38 – 7.21 (m, 5H), 7.05 – 7.01 (m, 1H), 6.48 (d, $J = 6.6$ Hz, 1H), 4.95 (s, 1H), 4.28 – 4.14 (m, 2H), 1.38 (s, 9H). ^1H NMR (400 MHz, CDCl_3 +TFAOMe) δ 8.19 (dd, $J = 7.8, 1.5$ Hz, 1H), 7.95 (d, $J = 7.9$ Hz, 1H), 7.77 (td, $J = 7.7, 1.7$ Hz, 1H), 7.68 (td, $J = 7.7, 1.3$ Hz, 1H), 7.48 (d, $J = 7.6$ Hz, 1H), 7.40 (td, $J = 8.1, 7.7, 1.3$ Hz, 1H), 7.37 – 7.32 (m, 1H), 7.29 – 7.22 (m, 3H), 7.10 (dd, $J = 7.9, 1.7$ Hz, 2H), 6.96 (d, $J = 8.0$ Hz, 1H), 4.77 (s, 2H), 4.25 (s, 1H), 4.08 (d, $J = 11.5$ Hz, 1H), 1.38 (s, 9H).

(M)-(S)-2-((tert-Butoxycarbonyl)amino)-2-phenylethyl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (M)-77

Purified by CC (hexane: EtOAc 5:1) Yield 21 mg (80%), amorphous solid ^1H NMR (400 MHz, CDCl_3) δ 8.16 (br. d, 1H), 7.97 – 7.92 (m, 1H), 7.79 – 7.73 (m, 1H), 7.68 (td, $J = 7.7, 1.3$ Hz, 1H), 7.50 – 7.44 (m, 1H), 7.42 – 7.32 (m, 2H), 7.32 – 7.22 (m, 3H), 7.26 (s, 4H), 7.16 – 7.10 (m, 2H), 6.97 – 6.93 (m, 1H), 4.79 (br. s, 1H), 4.68 (br. s, 1H), 4.27 (br. s, 1H), 4.08 (br. d, $J = 11.0$ Hz, 1H), 1.39 (s, 9H). ^{13}C NMR{ ^1H } (101 MHz, CDCl_3) δ 163.8, 155.1, 141.0 (app. d, $J = 38.7$ Hz), 140.7, 138.2, 137.6, 134.2, 133.8, 132.5, 130.6, 130.1, 128.8, 128.6, 127.9, 126.4, 126.0, 124.0, 121.7, 118.9 (app. d, $J = 272.0$ Hz), 110.7, 79.9, 67.2, 53.5, 28.3. ^{19}F NMR (376 MHz, CDCl_3) δ -61.98 HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd. For $\text{C}_{28}\text{H}_{27}\text{N}_3\text{O}_4\text{F}_3$; 526.1948; found: 526.1949. $[\alpha]_d^{22}$ -34.0° ($c=0.21$ CHCl_3). ^1H NMR (400 MHz, Acetone- D_6) δ 8.25 (ddd, $J = 7.9, 1.6, 0.4$ Hz, 1H), 7.95 (dd, $J = 7.7, 1.6$ Hz, 1H), 7.90 – 7.87 (m, 1H), 7.82 (td, $J = 7.7, 1.2$ Hz, 1H), 7.74 (dd, $J = 7.7, 1.0$ Hz, 1H), 7.45 – 7.37 (m, 2H), 7.34 – 7.29 (m, 4H), 7.28 – 7.24 (m, 1H), 7.02 – 6.99 (m, 1H), 6.49 (s, 1H), 4.91 (s, 1H), 4.23 (q, $J = 9.7, 8.4$ Hz, 1H), 4.15 (dd, $J = 10.5, 5.0$ Hz, 1H), 1.38 (s, 9H). ^1H NMR (400 MHz, CDCl_3 +TFAOMe) δ 8.18 – 8.14 (m, 1H), 7.94 (d, $J = 7.9$ Hz, 1H), 7.76 (td, $J = 7.7, 1.7$ Hz, 1H), 7.68 (td, $J = 7.7, 1.3$ Hz, 1H), 7.47 (d, $J = 7.3$ Hz, 1H), 7.40 (ddd, $J = 8.1, 7.2, 1.3$ Hz, 1H), 7.35 (td, $J = 7.7, 7.2, 1.2$ Hz, 1H), 7.31 – 7.24 (m, 3H), 7.12 (d, $J = 7.0$ Hz, 2H), 6.97 – 6.93 (m, 1H), 4.79 (s, 1H), 4.69 (d, $J = 7.3$ Hz, 1H), 4.26 (s, 1H), 4.09 (d, $J = 10.9$ Hz, 1H), 1.39 (s, 9H).

(S)-2-(6-Methoxynaphthalen-2-yl)propan-1-ol

(S)-2-(6-Methoxynaphthalen-2-yl)propanoic acid (150 mg, 0.652 mmol, 1 eq.) was slowly added into the suspension of LiAlH₄ (38 mg, 1.95 mmol, 3 eq.) in dry THF (12 ml). This mixture was stirred at room temperature for 16 hours. After 16 hours, EtOAc (30 ml) was added followed by deionized water (25 ml) and EtOAc (30 ml). Layers were separated and aq. layer was further extracted with EtOAc (3x 30ml). Combined organic phases were extracted with brine, dried with MgSO₄ and evaporated yielding white solid (123 mg, 87%) ¹H NMR (400 MHz, CDCl₃) δ 7.74 – 7.68 (m, *J* = 8.5, 6.2 Hz, 2H), 7.61 (d, *J* = 1.2 Hz, 1H), 7.35 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.17 – 7.11 (m, 1H), 3.92 (s, 3H), 3.77 (d, *J* = 6.8 Hz, 2H), 3.09 (h, *J* = 6.9 Hz, 1H), 1.36 (d, *J* = 7.0 Hz, 3H). ¹³C NMR{¹H} (101 MHz, CDCl₃) δ 157.6, 138.8, 133.7, 129.2, 129.2, 127.4, 126.4, 126.0, 119.0, 105.8, 68.8, 55.5, 42.5, 17.8. HRMS (ESI) *m/z*: [M+H]⁺ calcd. for: C₁₄H₁₇O₂: 217.1229 found: 217.1223 [α]_d²²: -19.86 (c= 0.7 CHCl₃).

P*-(S)-2-((tert-butoxycarbonyl)amino)-2-cyclohexylethyl benzo[d]imidazol-1-yl)benzoate (*P*)-78*2-(2-(trifluoromethyl)-1H-**

Purified by CC (Hexane: EtOAc 7:1), Yield: 12 mg (45%) ¹H NMR (400 MHz, CDCl₃) δ 8.31 – 8.26 (m, 1H), 7.98 – 7.94 (m, 1H), 7.77 (td, *J* = 7.6, 1.7 Hz, 1H), 7.70 (td, *J* = 7.6, 1.4 Hz, 1H), 7.46 – 7.43 (m, 1H), 7.38 (ddd, *J* = 8.4, 4.9, 1.4 Hz, 2H), 7.03 – 6.97 (m, 1H), 4.13 (d, *J* = 9.5 Hz, 1H), 4.11 – 4.07 (m, 1H), 3.97 (dd, *J* = 11.5, 3.5 Hz, 1H), 3.41 – 3.33 (m, 1H), 1.55 (t, *J* = 15.2 Hz, 3H), 1.42 (s, 9H), 1.07 – 0.93 (m, 3H), 0.85 – 0.73 (m, 2H), 0.63 – 0.52 (m, 1H). ¹³C NMR{¹H} (101 MHz, CDCl₃) δ 164.4, 155.8, 141.21 (q, *J* = 38.6 Hz), 140.8, 137.7, 133.9, 133.8, 133.1, 130.7, 130.1, 128.9, 126.2, 124.3, 121.7, 119.0 (q, *J* = 272.2 Hz), 111.0, 79.4, 66.0, 54.0, 37.9, 29.6, 29.1, 28.5, 26.2, 25.7, 25.7. ¹⁹F NMR (376 MHz, CDCl₃) δ -61.9. HRMS (ESI) *m/z*: [M + H]⁺ calcd. For C₂₈H₃₃N₃O₄F₃: 532.2418; found: 532.2418. [α]_d²² -60.83° (c= 0.12, CHCl₃) ¹H NMR (400 MHz, Acetone-D₆) δ 8.31 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.94 (td, *J* = 7.7, 1.6 Hz, 1H), 7.92 – 7.86 (m, 1H), 7.83 (td, *J* = 7.7, 1.2 Hz, 1H), 7.73 (d, *J* = 7.8 Hz, 1H), 7.47 – 7.40 (m, 2H), 7.09 (ddt, *J* = 7.8, 5.3, 2.2 Hz, 1H), 5.45 (d, *J* = 10.1 Hz, 1H), 4.03 (d, *J* = 5.3 Hz, 2H), 3.47 (h, *J* = 5.4, 4.8 Hz, 1H), 1.69 – 1.49 (m, 5H), 1.39 (s, 9H), 1.18 – 1.05 (m, 4H), 1.01 – 0.85 (m, 2H). ¹H NMR (400 MHz, CDCl₃+TFAOMe) δ 8.30 – 8.26 (m, 1H), 7.97 (d, *J* = 7.6 Hz, 1H), 7.77 (td, *J* = 7.6, 1.7 Hz, 1H), 7.70 (td, *J* = 7.6, 1.4 Hz, 1H), 7.45 (d, *J* = 6.4 Hz, 1H), 7.43 – 7.35 (m, 2H), 7.01 (d, *J* = 7.5 Hz, 1H), 4.13 (d, *J* = 9.7 Hz, 1H), 4.11 – 4.07 (m, 1H), 3.99 – 3.94 (m, 1H), 3.41 – 3.32 (m, 1H), 1.59 (d, *J* = 26.5 Hz, 4H), 1.42 (s, 9H), 1.35 (d, *J* = 10.9 Hz, 1H), 1.10 – 0.95 (m, 3H), 0.86 – 0.73 (m, 2H), 0.65 – 0.54 (m, 1H).

M*-(S)-2-((tert-butoxycarbonyl)amino)-2-cyclohexylethyl benzo[d]imidazol-1-yl)benzoate (*M*)-78*2-(2-(trifluoromethyl)-1H-**

Purified by CC (Hexane: EtOAc 7:1), Yield: 6 mg (22%) ¹H NMR (400 MHz, CDCl₃) δ 8.29 (dd, *J* = 7.6, 1.5 Hz, 1H), 8.00 – 7.95 (m, 1H), 7.76 (td, *J* = 7.6, 1.8 Hz, 1H), 7.71 (td, *J* = 7.6, 1.5 Hz, 1H), 7.47 – 7.37 (m, 3H), 7.05 – 7.02 (m, 1H), 4.15 (dd, *J* = 11.6, 4.5 Hz, 1H), 3.90 (dd, *J* = 11.6, 3.4 Hz, 1H), 3.55 (d, *J* = 9.6 Hz, 1H), 3.33 (dd, *J* = 10.6, 6.4 Hz, 1H), 1.67 (d, *J* = 19.2 Hz, 2H), 1.51 – 1.39 (m, 2H), 1.40 (s, 9H), 1.23 – 1.12 (m, 2H), 1.12 – 0.98 (m, 1H), 0.87 – 0.74 (m, 2H), 0.74 – 0.65 (m, 1H). ¹³C NMR{¹H} (101 MHz, CDCl₃) δ 164.6, 155.6, 141.12 (q, *J* = 39.3, 38.6 Hz), 140.7, 137.7, 137.7, 137.7, 133.8, 133.6, 133.2, 130.8, 130.3, 129.0, 126.4, 124.3, 121.8, 118.9 (q, *J* = 272.1 Hz), 110.9, 79.3, 66.2, 53.7, 37.8, 29.7, 29.2, 28.5, 26.2, 25.7, 25.6. ¹⁹F NMR (376 MHz, CDCl₃) δ -61.9. HRMS (ESI) *m/z*: [M + H]⁺ calcd. For C₂₈H₃₃N₃O₄F₃: 532.2418; found: 532.2420. [α]_d²² -63.08° (c= 0.6, CHCl₃) ¹H NMR (400 MHz, Acetone-D₆) δ 8.31 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.94 (td, *J* = 7.7, 1.6 Hz, 1H), 7.92 – 7.87 (m, 1H), 7.84 (td, *J* = 7.7, 1.2 Hz, 1H), 7.73 (d, *J* = 7.8 Hz, 1H), 7.48 – 7.41 (m, 2H), 7.10 – 7.06 (m, 1H), 5.21 (d, *J* = 9.4 Hz, 1H), 4.08 – 3.99 (m, 2H), 3.47 (h, *J* = 5.1, 4.5 Hz, 1H), 1.71 – 1.50 (m, 5H), 1.38 (s, 9H), 1.23 – 1.06 (m, 4H), 0.92 (dddd, *J* = 24.9, 16.3, 12.5, 3.6 Hz, 2H). ¹H NMR (400 MHz, CDCl₃+TFAOMe) δ 8.29 (dd, *J* = 7.6, 1.5 Hz, 1H), 8.00 – 7.96 (m, 1H), 7.76 (td, *J* = 7.6, 1.8 Hz, 1H), 7.71 (td, *J* = 7.6, 1.5 Hz, 1H), 7.42 (p, *J* = 7.1 Hz, 3H), 7.05 – 7.02 (m, 1H), 4.15 (dd, *J* = 11.5, 4.4 Hz, 1H), 3.90 (dd, *J* = 11.6, 3.4 Hz, 1H), 3.55 (d, *J* = 9.7 Hz, 1H), 3.37 – 3.29 (m, 1H), 1.72 – 1.58 (m, 3H), 1.46 (d, *J* = 8.4 Hz, 2H), 1.40 (s, 9H), 1.20 – 1.00 (m, 3H), 0.89 – 0.65 (m, 3H).

***P*-(*R*)-2-((*tert*-butoxycarbonyl)amino)-3-methylbutyl
benzo[d]imidazol-1-yl)benzoate (*P*)-79**

2-(2-(trifluoromethyl)-1H-

Purified by CC (Hexane: EtOAc 4:1), Yield: 12 mg (50%) ¹H NMR (400 MHz, CDCl₃) δ 8.27 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.96 (dd, *J* = 6.9, 1.5 Hz, 1H), 7.77 (td, *J* = 7.6, 1.8 Hz, 1H), 7.71 (td, *J* = 7.6, 1.4 Hz, 1H), 7.46 – 7.35 (m, 3H), 7.05 – 7.00 (m, 1H), 4.10 (dd, *J* = 11.5, 5.1 Hz, 1H), 3.92 (dd, *J* = 11.4, 4.0 Hz, 1H), 3.76 (d, *J* = 9.6 Hz, 1H), 3.34 (tt, *J* = 8.5, 4.4 Hz, 1H), 1.40 (s, 9H), 0.74 (dd, *J* = 13.3, 6.7 Hz, 6H). ¹³C NMR{¹H} (101 MHz, CDCl₃) δ 164.4, 155.6, 141.04 (q, *J* = 38.4, 37.9 Hz), 140.8, 137.7, 133.8, 133.0, 130.7, 130.2, 129.0, 126.3, 124.2, 121.8, 118.9 (q, *J* = 272.1 Hz), 110.9, 79.4, 66.3, 54.6, 28.8, 28.5, 19.4, 18.6. ¹⁹F NMR (376 MHz, CDCl₃) δ -62.0. δ HRMS (ESI) *m/z*: [M + H]⁺ calcd. For C₂₅H₂₉N₃O₄F₃: 492.2105; found: 492.2107. [α]_D²² -19.13° (*c* = 0.12 CHCl₃) ¹H NMR (400 MHz, Acetone-D₆) δ 8.31 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.95 (td, *J* = 7.7, 1.6 Hz, 1H), 7.91 – 7.86 (m, 1H), 7.83 (td, *J* = 7.7, 1.1 Hz, 1H), 7.75 – 7.72 (m, 1H), 7.46 – 7.39 (m, 2H), 7.09 – 7.04 (m, 1H), 5.51 (d, *J* = 9.5 Hz, 1H), 4.07 – 3.97 (m, 2H), 3.53 – 3.43 (m, 1H), 1.51 – 1.44 (m, 1H), 1.38 (s, 9H), 0.79 (d, *J* = 6.8 Hz, 6H). ¹H NMR (400 MHz, CDCl₃+TFAOMe) δ 8.29 – 8.23 (m, 1H), 7.96 (dd, *J* = 7.0, 1.5 Hz, 1H), 7.76 (td, *J* = 7.6, 1.8 Hz, 1H), 7.71 (td, *J* = 7.6, 1.4 Hz, 1H), 7.51 – 7.33 (m, 3H), 7.04 – 7.00 (m, 1H), 4.10 (dd, *J* = 11.5, 5.0 Hz, 1H), 3.92 (dd, *J* = 11.4, 4.0 Hz, 1H), 3.76 (d, *J* = 9.6 Hz, 1H), 3.34 (tt, *J* = 9.9, 4.8 Hz, 1H), 1.40 (s, 9H), 1.09 (dq, *J* = 14.1, 7.1 Hz, 1H), 0.74 (dd, *J* = 13.3, 6.7 Hz, 6H).

***M*-(*R*)-2-((*tert*-butoxycarbonyl)amino)-3-methylbutyl
benzo[d]imidazol-1-yl)benzoate (*M*)-79**

2-(2-(trifluoromethyl)-1H-

Purified by CC (Hexane: EtOAc 4:1), Yield: 12 mg (50%) ¹H NMR (400 MHz, CDCl₃) δ 8.27 (d, *J* = 7.8 Hz, 1H), 7.96 (ddd, *J* = 8.1, 1.4, 0.8 Hz, 1H), 7.77 (td, *J* = 7.6, 1.7 Hz, 1H), 7.70 (td, *J* = 7.7, 1.4 Hz, 1H), 7.45 (d, *J* = 7.3 Hz, 1H), 7.41 (ddd, *J* = 8.0, 7.2, 1.4 Hz, 1H), 7.42 – 7.31 (m, 1H), 7.00 (ddd, *J* = 7.9, 1.5, 0.8 Hz, 1H), 4.14 (d, *J* = 9.6 Hz, 1H), 4.08 (dd, *J* = 11.5, 5.8 Hz, 1H), 3.95 (dd, *J* = 11.5, 3.9 Hz, 1H), 3.43 – 3.30 (m, 1H), 1.41 (s, 9H), 0.68 (dd, *J* = 19.0, 6.7 Hz, 6H). ¹³C NMR{¹H} (101 MHz, CDCl₃) δ 164.3, 155.8, 141.1 (q, *J* = 38.6 Hz), 140.8, 137.7, 133.9, 133.8, 133.0, 130.7, 130.2, 128.9, 126.1, 124.1, 121.7, 119.0 (q, *J* = 272.2 Hz), 110.9, 79.4, 66.2, 54.7, 28.6, 28.4, 19.3, 18.6. ¹⁹F NMR (376 MHz, CDCl₃) δ -62.0. HRMS (ESI) *m/z*: [M + H]⁺ calcd. For C₂₅H₂₉N₃O₄F₃: 492.2105; found: 492.2104. [α]_D²² +84.35° (*c* = 0.12 CHCl₃) ¹H NMR (400 MHz, Acetone-D₆) δ 8.31 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.94 (td, *J* = 7.7, 1.6 Hz, 1H), 7.91 – 7.86 (m, 1H), 7.83 (td, *J* = 7.7, 1.2 Hz, 1H), 7.74 (d, *J* = 7.8 Hz, 1H), 7.46 – 7.39 (m, 2H), 7.11 – 7.05 (m, 1H), 5.58 (d, *J* = 9.4 Hz, 1H), 4.03 (d, *J* = 5.3 Hz, 2H), 3.54 – 3.45 (m, 1H), 1.50 – 1.43 (m, 1H), 1.38 (s, 9H), 0.80 (dd, *J* = 6.8, 2.4 Hz, 6H). ¹H NMR (400 MHz, CDCl₃+TFAOMe) δ 8.26 (d, *J* = 7.7 Hz, 1H), 7.94 (dd, *J* = 7.2, 1.1 Hz, 1H), 7.75 (td, *J* = 7.6, 1.7 Hz, 1H), 7.69 (td, *J* = 7.6, 1.4 Hz, 1H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.42 – 7.31 (m, 2H), 6.98 (dd, *J* = 7.2, 1.1 Hz, 1H), 4.12 (d, *J* = 9.3 Hz, 1H), 4.06 (dd, *J* = 11.4, 5.8 Hz, 1H), 3.98 – 3.88 (m, 1H), 3.40 – 3.30 (m, 1H), 1.40 (s, 9H), 0.91 (dt, *J* = 13.7, 6.9 Hz, 1H), 0.67 (dd, *J* = 19.0, 6.7 Hz, 6H).

***P*-(*S*)-2-((*tert*-butoxycarbonyl)amino)propyl
benzoate (*P*)-80**

2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-

Purified by CC (Hexane: EtOAc 4:1), Yield: 10 mg (40%) ¹H NMR (400 MHz,) δ 8.27 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.98 – 7.94 (m, 1H), 7.77 (td, *J* = 7.6, 1.7 Hz, 1H), 7.74 – 7.68 (m, 1H), 7.47 (dt, *J* = 5.4, 2.7 Hz, 1H), 7.44 – 7.34 (m, 2H), 7.03 – 6.98 (m, 1H), 4.06 (br.s, 1H), 3.92 (ddd, *J* = 12.8, 10.6, 3.4 Hz, 2H), 3.66 (br.s, *J* = 14.9 Hz, 1H), 1.41 (s, 9H), 0.69 (d, *J* = 5.0 Hz, 3H). ¹³C NMR{¹H} (101 MHz, CDCl₃) δ 164.3, 155.1, 140.73 (q, *J* = 39.3 Hz), 140.70, 137.7, 133.9, 133.8, 132.9, 130.7, 130.2, 128.9, 126.2, 124.2, 121.7, 118.9 (q, *J* = 272.9 Hz), 110.9, 68.6, 68.5, 45.2, 45.2, 28.5, 16.8. ¹⁹F NMR (376 MHz, CDCl₃) δ -62.0. HRMS (ESI) *m/z*: [M + H]⁺ calcd. For C₂₃H₂₅N₃O₄F₃: 464.1795; found: 464.1795. [α]_D²² -56.0° (*c* = 0.1 CHCl₃) ¹H NMR (400 MHz, Acetone-D₆) δ 8.32 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.95 (td, *J* = 7.7, 1.6 Hz, 1H), 7.90 – 7.86 (m, 1H), 7.84 (td, *J* = 7.7, 1.2 Hz, 1H), 7.76 – 7.72 (m, 1H), 7.45 – 7.37 (m, 2H), 7.11 – 7.05 (m, 1H), 5.64 (d, *J* = 5.6 Hz, 1H), 3.97 – 3.86 (m, 2H), 3.77 – 3.68 (m, 1H), 1.37 (s, 9H), 0.93 (d, *J* = 6.8 Hz, 3H). ¹H NMR (400 MHz, CDCl₃+TFAOMe) δ 8.27 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.97 – 7.93 (m, 1H), 7.77 (td, *J* = 7.6, 1.7 Hz, 1H), 7.71 (td, *J* = 7.7, 1.4 Hz, 1H), 7.47

(d, $J = 7.7$ Hz, 1H), 7.43 – 7.34 (m, 2H), 7.00 (ddd, $J = 7.6, 1.5, 0.7$ Hz, 1H), 4.08 (d, $J = 5.8$ Hz, 1H), 3.96 – 3.86 (m, 2H), 3.66 (s, 1H), 1.41 (s, 9H), 0.69 (d, $J = 5.3$ Hz, 3H).

***M*-(*S*)-2-((*tert*-butoxycarbonyl)amino)propyl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (*M*)-80**

Purified by CC (Hexane: EtOAc 4:1), Yield: 14 mg (60%) $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.25 (dd, $J = 7.8, 1.6$ Hz, 1H), 7.95 (dt, $J = 6.9, 4.0$ Hz, 1H), 7.76 (td, $J = 7.6, 1.7$ Hz, 1H), 7.70 (td, $J = 7.7, 1.4$ Hz, 1H), 7.45 (d, $J = 7.7$ Hz, 1H), 7.43 – 7.33 (m, 2H), 7.01 – 6.97 (m, 1H), 3.96 (br.s., $J = 20.9$ Hz, 2H), 3.84 (dd, $J = 11.0, 4.2$ Hz, 1H), 3.66 (s, 1H), 1.39 (s, 9H), 0.78 (s, 3H). $^{13}\text{C NMR}\{^1\text{H}\}$ (101 MHz, CDCl_3) δ 164.3, 155.0, 141.09 (q, $J = 37.8$ Hz), 140.8, 137.7, 133.9, 133.8, 132.9, 130.7, 130.2, 129.0, 126.2, 124.2, 121.7, 119.0 (q, $J = 272.0$ Hz), 110.8, 68.7, 28.5, 17.1. $^{19}\text{F NMR}$ (376 MHz, CDCl_3) δ -61.95. **HRMS** (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd. For $\text{C}_{23}\text{H}_{25}\text{N}_3\text{O}_4\text{F}_3$: 464.1795; found: 464.1793. $[\alpha]_d^{22} +13.57^\circ$ ($c = 0.14$ CHCl_3) $^1\text{H NMR}$ (400 MHz, Acetone- d_6) δ 8.33 (dd, $J = 7.8, 1.6$ Hz, 1H), 7.95 (td, $J = 7.7, 1.6$ Hz, 1H), 7.90 – 7.87 (m, 1H), 7.84 (td, $J = 7.7, 1.2$ Hz, 1H), 7.77 – 7.72 (m, 1H), 7.45 – 7.38 (m, 2H), 7.09 – 7.04 (m, 1H), 5.67 (d, $J = 5.6$ Hz, 1H), 3.92 (dd, $J = 6.8, 3.9$ Hz, 2H), 3.71 (dt, $J = 9.5, 5.4$ Hz, 1H), 1.38 (s, 9H), 0.90 (d, $J = 6.4$ Hz, 3H). $^1\text{H NMR}$ (400 MHz, $\text{CDCl}_3 + \text{TFAOMe}$) δ 8.25 (dd, $J = 7.7, 1.7$ Hz, 1H), 7.96 – 7.93 (m, 1H), 7.76 (td, $J = 7.6, 1.7$ Hz, 1H), 7.70 (td, $J = 7.7, 1.4$ Hz, 1H), 7.46 – 7.44 (m, 1H), 7.37 (pd, $J = 7.2, 1.3$ Hz, 2H), 7.01 – 6.97 (m, 1H), 3.94 – 3.91 (m, 2H), 3.84 (dd, $J = 11.0, 4.4$ Hz, 1H), 3.66 (s, 1H), 1.39 (s, 9H), 0.78 (s, 3H).

***P*-(*S*)-2-((*tert*-butoxycarbonyl)amino)-3-phenylpropyl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (*P*)-81**

Purified by CC (Hexane: EtOAc 4:1), Yield: 21 mg (95%) $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.28 (d, $J = 7.5$ Hz, 1H), 7.99 – 7.93 (m, 1H), 7.79 (td, $J = 7.6, 1.7$ Hz, 1H), 7.72 (td, $J = 7.7, 1.4$ Hz, 1H), 7.48 (d, $J = 7.7$ Hz, 1H), 7.43 – 7.36 (m, 2H), 7.24 – 7.13 (m, 3H), 7.08 – 7.03 (m, 1H), 6.90 (d, $J = 6.9$ Hz, 2H), 4.19 (d, $J = 7.4$ Hz, 1H), 3.94 (d, $J = 4.5$ Hz, 2H), 3.81 (br. s, 1H), 2.37 (dd, $J = 13.5, 6.3$ Hz, 1H), 2.04 (dd, $J = 13.0, 8.0$ Hz, 1H), 1.40 (s, 9H). $^{13}\text{C NMR}\{^1\text{H}\}$ (101 MHz, CDCl_3) δ 164.3, 155.2, 141.2 (q, $J = 39.3$ Hz), 140.8, 137.7, 137.1, 133.9, 133.9, 133.1, 130.8, 130.2, 129.2, 128.8, 128.6, 126.7, 126.3, 124.3, 123.0, 119.0 (q, $J = 271.7$ Hz), 110.9, 79.6, 66.5, 50.5, 37.0, 28.4. $^{19}\text{F NMR}$ (376 MHz, CDCl_3) δ -61.9., **HRMS** (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd. For $\text{C}_{29}\text{H}_{29}\text{N}_3\text{O}_4\text{F}_3$: 440.2105; found: 440.2108. $[\alpha]_d^{22} -26.19^\circ$ ($c = 0.21$ CHCl_3) $^1\text{H NMR}$ (400 MHz, Acetone- D_6) δ 8.34 (dd, $J = 7.9, 1.4$ Hz, 1H), 7.95 (td, $J = 7.7, 1.6$ Hz, 1H), 7.91 – 7.87 (m, 1H), 7.84 (td, $J = 7.7, 1.2$ Hz, 1H), 7.75 (d, $J = 7.8$ Hz, 1H), 7.44 – 7.39 (m, 2H), 7.24 (t, $J = 7.2$ Hz, 2H), 7.19 – 7.09 (m, 4H), 5.66 (d, $J = 8.4$ Hz, 1H), 4.00 – 3.97 (m, 2H), 3.93 (dd, $J = 11.6, 6.0$ Hz, 1H), 2.59 (q, $J = 7.3, 6.8$ Hz, 2H), 1.33 (s, 9H). $^1\text{H NMR}$ (400 MHz, $\text{CDCl}_3 + \text{TFAOMe}$) δ 8.27 (d, $J = 7.4$ Hz, 1H), 7.99 – 7.94 (m, 1H), 7.79 (td, $J = 7.6, 1.7$ Hz, 1H), 7.72 (td, $J = 7.7, 1.4$ Hz, 1H), 7.48 (d, $J = 7.4$ Hz, 1H), 7.43 – 7.36 (m, 2H), 7.19 (dt, $J = 11.8, 6.8$ Hz, 3H), 7.09 – 7.03 (m, 1H), 6.90 (d, $J = 6.8$ Hz, 2H), 4.19 (d, $J = 9.1$ Hz, 1H), 3.94 (d, $J = 4.5$ Hz, 2H), 3.81 (s, 1H), 2.37 (dd, $J = 13.8, 6.5$ Hz, 1H), 2.04 (t, $J = 9.9$ Hz, 1H), 1.40 (s, 9H).

***M*-(*S*)-2-((*tert*-butoxycarbonyl)amino)-3-phenylpropyl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (*M*)-81**

Purified by CC (Hexane: EtOAc 4:1), Yield: 15 mg (40%) $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.26 (dd, $J = 7.8, 1.6$ Hz, 1H), 7.98 – 7.92 (m, 1H), 7.79 (td, $J = 7.6, 1.7$ Hz, 1H), 7.75 – 7.70 (m, 1H), 7.48 (dd, $J = 7.7, 0.9$ Hz, 1H), 7.43 – 7.36 (m, 2H), 7.26 – 7.15 (m, 3H), 7.05 – 6.97 (m, 3H), 3.96 (br.s., $J = 11.2$ Hz, 2H), 3.89 (dd, $J = 11.3, 4.2$ Hz, 1H), 3.72 (br.s., $J = 23.2$ Hz, 1H), 2.54 – 2.30 (m, 2H), 1.38 (s, 9H). $^{13}\text{C NMR}\{^1\text{H}\}$ (101 MHz, CDCl_3) δ 164.3, 155.1, 141.13 (q, $J = 38.5$ Hz), 140.7, 137.7, 137.2, 133.9, 133.8, 132.9, 130.8, 130.2, 129.2, 128.9, 128.7, 126.7, 126.4, 124.3, 121.8, 119.0 (q, $J = 272.1$ Hz), 110.8, 79.6, 66.6, 50.5, 37.2, 28.4. $^{19}\text{F NMR}$ (376 MHz, CDCl_3) δ -61.8. **HRMS** (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd. For $\text{C}_{29}\text{H}_{29}\text{N}_3\text{O}_4\text{F}_3$: 440.2105; found: 440.2109. $[\alpha]_d^{22} +21.0^\circ$ ($c = 0.15$ CHCl_3) $^1\text{H NMR}$ (400 MHz, Acetone- D_6) δ 8.34 (dd, $J = 7.8, 1.5$ Hz, 1H), 7.96 (td, $J = 7.7, 1.6$ Hz, 1H), 7.89 – 7.83 (m, 2H), 7.75 (dd, $J = 7.8, 1.1$ Hz, 1H), 7.44 – 7.38 (m, 2H), 7.24 (tt, $J = 8.1, 1.7$ Hz, 2H), 7.20 – 7.16 (m, 1H), 7.16 – 7.11 (m, 2H), 7.10 – 7.07 (m, 1H), 5.68 (d, $J = 8.1$ Hz, 1H), 3.99 (qd, $J = 11.0, 5.3$ Hz, 2H), 3.93 – 3.86

(m, 1H), 2.62 (d, $J = 7.1$ Hz, 2H), 1.33 (s, 9H). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.26 (dd, $J = 7.8, 1.6$ Hz, 1H), 7.97 – 7.94 (m, 1H), 7.79 (td, $J = 7.6, 1.7$ Hz, 1H), 7.73 (td, $J = 7.6, 1.4$ Hz, 1H), 7.48 (dd, $J = 7.7, 1.0$ Hz, 1H), 7.43 – 7.36 (m, 2H), 7.23 (tt, $J = 8.0, 2.0$ Hz, 2H), 7.20 – 7.15 (m, 1H), 7.05 – 6.98 (m, 3H), 3.98 (d, $J = 12.6$ Hz, 2H), 3.89 (dd, $J = 11.3, 4.2$ Hz, 1H), 3.74 (s, 1H), 2.53 – 2.43 (m, 1H), 2.36 (dd, $J = 11.5, 8.9$ Hz, 1H), 1.38 (s, 9H).

***P*-(*R*)-2-((*tert*-butoxycarbonyl)amino)-4-methylpentyl benzo[d]imidazol-1-yl)benzoate (*P*)-82**

2-(2-(trifluoromethyl)-1H-

Purified by CC (Hexane: EtOAc 5:1), Yield: 13 mg (50%) $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.28 (d, $J = 7.4$ Hz, 1H), 7.96 (dd, $J = 7.2, 1.1$ Hz, 1H), 7.77 (td, $J = 7.6, 1.7$ Hz, 1H), 7.71 (td, $J = 7.7, 1.3$ Hz, 1H), 7.41 (ddd, $J = 18.2, 16.2, 7.7$ Hz, 3H), 7.01 (dd, $J = 7.1, 1.1$ Hz, 1H), 3.99 (dd, $J = 11.0, 4.2$ Hz, 1H), 3.90 (dd, $J = 11.3, 3.6$ Hz, 1H), 3.70 (d, $J = 8.5$ Hz, 1H), 3.60 (dd, $J = 7.4, 3.5$ Hz, 1H), 1.46 – 1.41 (m, 1H), 1.40 (s, 9H), 0.96 – 0.87 (m, 1H), 0.85 (d, $J = 6.6$ Hz, 3H), 0.81 (d, $J = 7.0$ Hz, 3H). $^{13}\text{C NMR}\{^1\text{H}\}$ (126 MHz, CDCl_3) δ 164.5, 155.2, 141.1 (q, $J = 38.3$ Hz), 140.7, 137.7, 133.8, 133.0, 130.7, 130.2, 129.0, 126.3, 124.3, 121.8, 119.0 (q, $J = 272.2$ Hz), 115.7, 110.9, 79.4, 68.3, 47.5, 39.9, 28.5, 24.8, 22.8, 22.0. $^{19}\text{F NMR}$ (376 MHz, CDCl_3) δ -61.88 **HRMS** (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd. For $\text{C}_{26}\text{H}_{31}\text{N}_3\text{O}_4\text{F}_3$: 506.2161; found: 506.2162. $[\alpha]_D^{22}$ -10.77° ($c = 0.13$, CHCl_3) $^1\text{H NMR}$ (400 MHz, Acetone- D_6) δ 8.33 (dd, $J = 7.8, 1.5$ Hz, 1H), 7.94 (td, $J = 7.7, 1.6$ Hz, 1H), 7.91 – 7.86 (m, 1H), 7.86 – 7.81 (m, 1H), 7.73 (d, $J = 7.8$ Hz, 1H), 7.46 – 7.39 (m, 2H), 7.09 – 7.04 (m, 1H), 5.47 (d, $J = 8.8$ Hz, 1H), 3.93 (dt, $J = 9.0, 4.2$ Hz, 2H), 3.79 (dq, $J = 8.5, 4.6, 3.8$ Hz, 1H), 1.63 – 1.52 (m, 1H), 1.38 (s, 9H), 1.25 – 1.17 (m, 1H), 1.04 (ddd, $J = 13.6, 8.9, 4.6$ Hz, 1H), 0.85 (dd, $J = 11.3, 6.6$ Hz, 6H). $^1\text{H NMR}$ (400 MHz, $\text{CDCl}_3 + \text{TFAOMe}$) δ 8.28 (d, $J = 7.7$ Hz, 1H), 7.97 (d, $J = 7.7$ Hz, 1H), 7.77 (td, $J = 7.6, 1.8$ Hz, 1H), 7.71 (td, $J = 7.6, 1.4$ Hz, 1H), 7.46 – 7.36 (m, 3H), 7.02 (d, $J = 7.8$ Hz, 1H), 4.02 – 3.98 (m, 1H), 3.90 (dd, $J = 11.2, 3.6$ Hz, 1H), 3.71 (d, $J = 9.1$ Hz, 1H), 3.64 – 3.57 (m, 1H), 1.45 – 1.42 (m, 1H), 1.40 (s, 9H), 0.89 (d, $J = 5.4$ Hz, 1H), 0.83 (dd, $J = 15.6, 6.6$ Hz, 7H).

***M*-(*R*)-2-((*tert*-butoxycarbonyl)amino)-4-methylpentyl benzo[d]imidazol-1-yl)benzoate (*M*)-82**

2-(2-(trifluoromethyl)-1H-

Purified by CC (Hexane: EtOAc 5:1), Yield: 8 mg (30%) $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.29 (d, $J = 7.6$ Hz, 1H), 7.98 – 7.95 (m, 1H), 7.77 (td, $J = 7.6, 1.6$ Hz, 1H), 7.71 (td, $J = 7.7, 1.3$ Hz, 1H), 7.45 (d, $J = 7.7$ Hz, 1H), 7.43 – 7.39 (m, 1H), 7.37 (ddd, $J = 8.3, 7.2, 1.3$ Hz, 1H), 7.02 – 7.00 (m, 1H), 3.96 (t, $J = 5.9$ Hz, 3H), 3.64 (dq, $J = 8.8, 4.7$ Hz, 1H), 1.42 (s, 9H), 1.39 – 1.34 (m, 1H), 0.77 (d, $J = 7.0$ Hz, 3H), 0.74 (d, $J = 6.6$ Hz, 3H), 0.72 – 0.64 (m, 1H). $^{13}\text{C NMR}\{^1\text{H}\}$ (126 MHz, CDCl_3) δ 164.4, 155.4, 141.2 (q, $J = 38.1$ Hz), 140.8, 137.7, 133.9, 133.8, 133.1, 130.7, 130.1, 129.0, 126.2, 124.2, 121.8, 119.0 (q, $J = 272.3$ Hz), 111.0, 79.4, 68.2, 47.6, 39.6, 28.5, 24.7, 22.9, 22.0. $^{19}\text{F NMR}$ (376 MHz, CDCl_3) δ -61.94 **HRMS** (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd. For $\text{C}_{26}\text{H}_{31}\text{N}_3\text{O}_4\text{F}_3$: 506.2161; found: 506.2163. $[\alpha]_D^{22}$ +85.00° ($c = 0.8$, CHCl_3) $^1\text{H NMR}$ (400 MHz, Acetone- D_6) δ 8.32 (dd, $J = 7.8, 1.6$ Hz, 1H), 7.94 (td, $J = 7.7, 1.5$ Hz, 1H), 7.91 – 7.86 (m, 1H), 7.86 – 7.81 (m, 1H), 7.74 (d, $J = 7.8$ Hz, 1H), 7.46 – 7.39 (m, 2H), 7.11 – 7.07 (m, 1H), 5.51 (d, $J = 8.8$ Hz, 1H), 3.93 (d, $J = 5.4$ Hz, 2H), 3.77 (dt, $J = 10.4, 5.2$ Hz, 1H), 1.67 – 1.52 (m, 1H), 1.38 (s, 9H), 1.24 – 1.13 (m, 1H), 1.01 (ddd, $J = 13.7, 9.1, 4.6$ Hz, 1H), 0.86 – 0.80 (m, 6H). $^1\text{H NMR}$ (400 MHz, $\text{CDCl}_3 + \text{TFAOMe}$) δ 8.29 (d, $J = 7.3$ Hz, 1H), 7.98 – 7.93 (m, 1H), 7.77 (td, $J = 7.6, 1.7$ Hz, 1H), 7.71 (td, $J = 7.6, 1.4$ Hz, 1H), 7.45 (d, $J = 7.6$ Hz, 1H), 7.44 – 7.35 (m, 3H), 7.01 (dt, $J = 7.7, 0.9$ Hz, 1H), 3.97 – 3.93 (m, 3H), 3.69 – 3.58 (m, 1H), 1.42 (s, 9H), 0.76 (dd, $J = 12.2, 6.6$ Hz, 7H), 0.70 (d, $J = 12.0$ Hz, 1H).

***P*-(*S*)-3-(benzyloxy)-2-((*tert*-butoxycarbonyl)amino)propyl benzo[d]imidazol-1-yl)benzoate (*P*)-83**

2-(2-(trifluoromethyl)-1H-

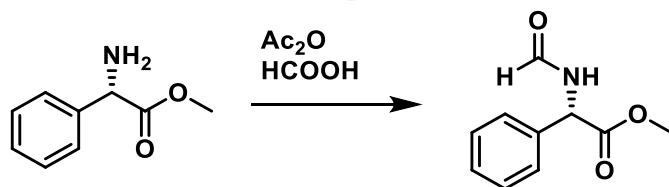
Purified by CC (Hexane: EtOAc 3:1), Yield: 23 mg (80%) $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.23 (d, $J = 7.9$ Hz, 1H), 7.94 (d, $J = 7.6$ Hz, 1H), 7.77 (td, $J = 7.7, 1.6$ Hz, 1H), 7.68 (td, $J = 7.7, 1.2$ Hz, 1H), 7.45 (d, $J = 7.6$ Hz, 1H), 7.42 – 7.37 (m, 1H), 7.35 (dd, $J = 8.0, 1.1$ Hz, 2H), 7.33 – 7.26 (m, 3H), 7.23 – 7.19 (m, 2H), 6.95 (d, $J = 7.7$ Hz, 1H), 4.54 (d, $J = 10.8$ Hz, 1H), 4.32 (s, $J = 12.7$ Hz, 2H), 4.15 (dd, $J = 10.9, 5.5$ Hz, 1H), 4.02 (dd, $J = 11.1, 5.3$ Hz, 1H), 3.78 – 3.69 (m, 1H), 3.13 – 2.99 (m, 2H), 1.41 (s,

9H). $^{13}\text{C NMR}\{^1\text{H}\}$ (101 MHz, CDCl_3) δ 164.0, 155.3, 141.09 (q, $J = 37.8$ Hz) 140.7, 137.8, 137.6, 134.0, 133.8, 132.9, 130.7, 130.1, 128.9, 128.5, 127.9, 127.8, 126.1, 124.2, 121.7, 118.9 (q, $J = 272.1$ Hz), 110.9, 79.7, 73.3, 68.4, 65.0, 49.0, 28.4. $^{19}\text{F NMR}$ (376 MHz, CDCl_3) δ -62.0. **HRMS** (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd. For $\text{C}_{30}\text{H}_{31}\text{N}_3\text{O}_5\text{F}_3$; 570.2210; found: 570.2214. $[\alpha]_d^{22}$ -29.13° ($c = 0.23$ CHCl_3) $^1\text{H NMR}$ (400 MHz, Acetone- D_6) δ 8.28 (ddd, $J = 7.8, 1.6, 0.3$ Hz, 1H), 7.94 (td, $J = 7.7, 1.6$ Hz, 1H), 7.90 – 7.86 (m, 1H), 7.82 (td, $J = 7.7, 1.3$ Hz, 1H), 7.73 (d, $J = 7.8$ Hz, 1H), 7.44 – 7.37 (m, 2H), 7.33 – 7.23 (m, 5H), 7.08 – 7.01 (m, 1H), 5.65 (d, $J = 8.5$ Hz, 1H), 4.42 (s, 2H), 4.14 – 4.05 (m, 2H), 3.93 – 3.83 (m, 1H), 3.36 – 3.25 (m, 2H), 1.38 (s, 9H). $^1\text{H NMR}$ (400 MHz, $\text{CDCl}_3 + \text{TFAOMe}$) δ 8.22 (d, $J = 7.6$ Hz, 1H), 7.94 (dt, $J = 8.5, 0.8$ Hz, 1H), 7.76 (td, $J = 7.6, 1.7$ Hz, 1H), 7.68 (td, $J = 7.7, 1.3$ Hz, 1H), 7.45 (d, $J = 7.3$ Hz, 1H), 7.42 – 7.36 (m, 1H), 7.35 (dd, $J = 8.0, 1.3$ Hz, 1H), 7.33 – 7.25 (m, 3H), 7.23 – 7.19 (m, 2H), 6.95 (d, $J = 7.6$ Hz, 1H), 4.55 (d, $J = 8.5$ Hz, 1H), 4.32 (s, 2H), 4.15 (dd, $J = 10.8, 5.8$ Hz, 1H), 4.02 (dd, $J = 9.9, 3.9$ Hz, 1H), 3.75 (s, 1H), 3.15 – 2.99 (m, 2H), 1.41 (s, 9H).

***M*-(*S*)-3-(benzyloxy)-2-((*tert*-butoxycarbonyl)amino)propyl 2-(2-(trifluoromethyl)-1H-benzo[*d*]imidazol-1-yl)benzoate (*M*)-83**

Purified by CC (Hexane: EtOAc 3:1), Yield: 28 mg (95%) $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.22 (d, $J = 7.6$ Hz, 1H), 7.94 (d, $J = 8.0$ Hz, 1H), 7.77 (td, $J = 7.6, 1.6$ Hz, 1H), 7.69 (t, $J = 7.5$ Hz, 1H), 7.45 (dd, $J = 7.8, 1.1$ Hz, 1H), 7.39 (ddd, $J = 8.1, 5.8, 1.3$ Hz, 1H), 7.37 – 7.33 (m, 1H), 7.33 – 7.26 (m, 3H), 7.23 – 7.18 (m, $J = 6.3$ Hz, 2H), 6.95 (d, $J = 7.8$ Hz, 1H), 4.49 (d, $J = 8.0$ Hz, 1H), 4.34 (dd, $J = 24.6, 11.4$ Hz, 2H), 4.09 (t, $J = 13.1$ Hz, 1H), 3.99 (dt, $J = 13.5, 6.7$ Hz, 1H), 3.77 (s, 1H), 3.12 (d, $J = 31.8$ Hz, 2H), 1.41 (s, 9H). $^{13}\text{C NMR}\{^1\text{H}\}$ (101 MHz, CDCl_3) δ 164.0, 155.2, 141.0 (q, $J = 38.6$ Hz), 140.7, 137.9, 137.7, 133.9, 133.8, 132.9, 130.7, 130.2, 128.9, 128.5, 127.9, 127.7, 126.2, 124.2, 121.7, 118.9 (q, $J = 272.1$ Hz), 110.8, 79.7, 73.2, 68.3, 64.7, 48.9, 28.4. $^{19}\text{F NMR}$ (376 MHz,) δ -61.9. **HRMS** (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd. For $\text{C}_{30}\text{H}_{31}\text{N}_3\text{O}_5\text{F}_3$; 570.2210; found: 570.2215. $[\alpha]_d^{22}$ +9.29° ($c = 0.28$ CHCl_3) $^1\text{H NMR}$ (400 MHz, Acetone- D_6) δ 8.28 – 8.25 (m, 1H), 7.92 (td, $J = 7.7, 1.6$ Hz, 1H), 7.86 – 7.83 (m, 1H), 7.80 (td, $J = 7.8, 1.2$ Hz, 1H), 7.71 (dd, $J = 7.9, 0.9$ Hz, 1H), 7.41 – 7.34 (m, 2H), 7.29 – 7.19 (m, 5H), 6.99 (dd, $J = 6.4, 2.3$ Hz, 1H), 5.68 (d, $J = 8.7$ Hz, 1H), 4.41 – 4.27 (m, 2H), 4.05 (qd, $J = 11.1, 6.3$ Hz, 2H), 3.76 (p, $J = 7.4, 6.3$ Hz, 1H), 3.26 – 3.10 (m, 2H), 1.35 (s, 9H). $^1\text{H NMR}$ (400 MHz, $\text{CDCl}_3 + \text{TFAOMe}$) δ 8.21 (d, $J = 7.5$ Hz, 1H), 7.94 (d, $J = 7.9$ Hz, 1H), 7.77 (td, $J = 7.7, 1.6$ Hz, 1H), 7.68 (t, $J = 7.4$ Hz, 1H), 7.45 (dd, $J = 7.8, 1.0$ Hz, 1H), 7.41 – 7.36 (m, 1H), 7.36 – 7.33 (m, 1H), 7.32 – 7.26 (m, 3H), 7.21 (d, $J = 6.4$ Hz, 2H), 6.95 (d, $J = 7.9$ Hz, 1H), 4.49 (d, $J = 8.3$ Hz, 1H), 4.34 (q, $J = 11.4$ Hz, 2H), 4.11 (s, 1H), 4.01 (dd, $J = 6.7, 4.2$ Hz, 1H), 3.75 (s, 1H), 3.11 (d, $J = 33.7$ Hz, 2H), 1.41 (s, 9H).

Methyl (*S*)-2-formamido-2-phenylacetate (85)

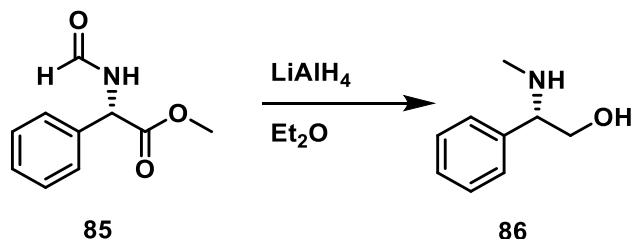


85

Following literature procedure.¹⁷⁰ (*S*)-phenylglycine methyl ester hydrochloride (603 mg, 3 mmol, 1 eq.) was dissolved in DI water (10 ml) and aq. K_2CO_3 solution was added (10ml, 10 weight %). The solution was extracted with diethyl ether (3x 20 mL), dried with MgSO_4 and evaporated to yield of freebase (*S*)-phenylglycine methyl ester (360 mg of clear oil (70%)). This oil was dissolved in formic acid (30 mL) and cooled in ice bath. Acetic anhydride (8.3 mL) was added dropwise while cooling. After the addition was complete, the reaction was stirred for 16 hours. After 16 hours, DI water was added (20 mL) and the solution was stirred for 20 minutes and evaporated. The oily residue was dissolved in EtOAc (50 mL) and extracted with 10% aq. HCl (3x 50 mL) and 10% aq. K_2CO_3 (3x 50 mL), dried with MgSO_4 and evaporated to yield clear oil which solidified upon standing on room temperature or under high vacuum. Yield: 371 mg of white solid (75%). Reaction was reproduced on 10 mmol scale, yielding 1.2g (65%) of white solid. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.25 (s, 1H), 7.38 – 7.33 (m, 5H), 6.60 (s, 1H),

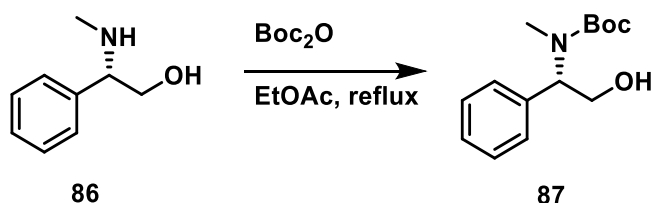
5.67 (d, $J = 7.4$ Hz, 1H), 3.75 (s, 3H). $^{13}\text{C NMR}$ $\{^1\text{H}\}$ (101 MHz, CDCl_3) δ 171.1, 160.2, 136.2, 129.2, 128.9, 127.3, 55.2, 53.1. **HRMS** (ESI- TOF) m/z : $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{10}\text{H}_{12}\text{N}_3\text{O}_1$: 194.0812; found: 194.0813, $[\alpha]_d^{22} +87.62^\circ$ ($c = 0.42$, CHCl_3)

(S)-2-(methylamino)-2-phenylethan-1-ol (86)



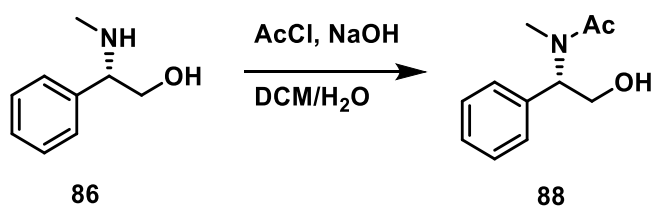
Modified literature procedure.¹⁷⁰ Methyl (*S*)-2-formamido-2-phenylacetate (400 mg, 2 mmol, 1 eq.) was added portion wise to a suspension of LiAlH_4 (380 mg, 10 mmol, 5eq.) in dry THF (15 mL) at 5°C (ice/water bath). After addition was completed, the mixture was refluxed for 16 h. After reaction completion (TLC: EtOAc: MeOH 2:1), reaction was cooled to room temperature and further cooled in ice bath and aq. NaOH solution (15% by weight, 0.75 ml/ mmol LiAlH_4) was added dropwise. The resulting suspension was filtered through celite and washed thoroughly with EtOAc, dried by MgSO_4 and evaporated. The residual oil was purified by column chromatography (EtOAc: MeOH 2:1) yielding 242 mg of white solid (80%). Reaction was reproduced on 6.2 mmol scale, yielding white solid which was suspended in chloroform, filtered and after evaporation 800 mg (85%) of white solid was obtained. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.39 – 7.34 (m, 2H), 7.32 – 7.27 (m, 3H), 3.75 (dd, $J = 10.1, 4.1$ Hz, 1H), 3.71 – 3.66 (m, 1H), 3.61 (dd, $J = 10.0, 8.0$ Hz, 1H), 2.69 (s, 2H), 2.36 (s, 3H). $^{13}\text{C NMR}$ $\{^1\text{H}\}$ (101 MHz, CDCl_3) δ 179.1, 129.4, 129.2, 128.2, 66.2, 64.5, 31.5, 23.8. **HRMS** (ESI- TOF) m/z : $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_9\text{H}_4\text{N}_1\text{O}_1$: 152.1070; found: 152.1070, $[\alpha]_d^{22} +39.89^\circ$ ($c = 0.88$, CHCl_3)

tert-Butyl (S)-(2-hydroxy-1-phenylethyl)(methyl)carbamate (87)



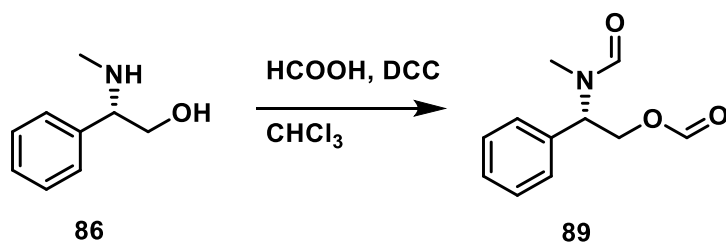
Following literature procedure.¹⁷¹ (*S*)-2-(methylamino)-2-phenylethan-1-ol (40 mg, 0.25 mmol, 1 eq.) was dissolved in EtOAc (10 mL) and Boc_2O was added at once and the mixture was refluxed for 16 hours. After 16 hours, the reaction was cooled to room temperature washed twice with water and once with brine, dried with MgSO_4 and evaporated, yielding 53 mg of oil (85%) $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.36 – 7.20 (m, 5H), 5.32 – 5.24 (m, 1H), 4.11 – 4.01 (m, 2H), 2.69 (s, 1H), 1.51 (s, 3H), 1.47 (s, 9H). $^{13}\text{C NMR}$ $\{^1\text{H}\}$ (101 MHz, CDCl_3) δ 146.9, 128.8, 127.8, 127.5, 85.3, 80.4, 60.6, 28.6, 27.6. **HRMS** (ESI- TOF) m/z : $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{14}\text{H}_{22}\text{N}_1\text{O}_3$: 252.1594; found: 252.1595, $[\alpha]_d^{22} +55.17^\circ$ ($c = 0.6$, CHCl_3)

(S)-N-(2-hydroxy-1-phenylethyl)-N-methylacetamide (88)



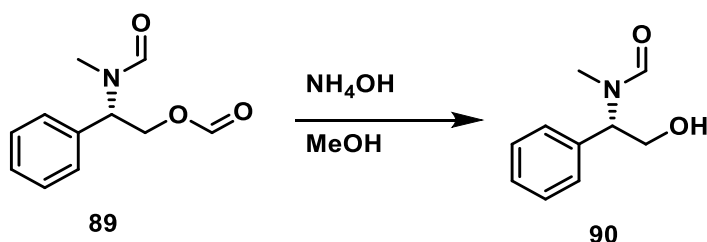
Following literature procedure.¹⁷² (S)-N-methyl-phenylglycinol (50 mg, 0.33 mmol, 1 eq.) was dissolved in DCM (1.5 mL) and acetyl chloride was added (30 μ L, 0.4 mmol, 1.2 eq.) followed by dropwise addition of 0.5M NaOH (840 μ L, 0.4 mmol, 1.2 eq.). The biphasic system was stirred rapidly for 1 hour. After 1 hour, the mixture was diluted with water (10 mL) and extracted with DCM (3 \times 10 mL). Organic layers were combined, dried with MgSO₄ and purified by column chromatography (EtOAc: MeOH 20:1) to yield 50 mg of white solid (78%) as a mixture of rotamers in approx. 10:4 ratio. Peaks belonging to major rotamer are designated M, peaks belonging to minor rotamer are designated m. ¹H NMR (400 MHz, CDCl₃) δ 7.41 – 7.19 (m, 10H, both rotamers), 5.83 (dd, *J* = 9.3, 4.9 Hz, 1H, M), 5.09 (dd, *J* = 9.2, 4.9 Hz, 1H, m), 4.23 – 4.02 (m, 4H, both rotamers), 2.78 (s, 4H, both rotamers), 2.42 (dd, *J* = 7.2, 4.7 Hz, 1H, M), 2.28 (s, 3H, m), 2.19 (s, 3H, M), 2.15 – 2.05 (m, 1H, m). ¹³C NMR {¹H} (126 MHz, CDCl₃) δ 172.8 M, 172.4 m, 137.2 M, 137.0 m, 129.1 m, 128.8 M, 128.2 m, 127.93 M, 127.89 M, 127.0 m, 62.6 m, 61.9 M, 61.5 m, 58.4 M, 32.0 M, 28.1 m, 22.5 M, 22.2 m. HRMS (ESI) *m/z*: [M+H]⁺ calcd. for: C₁₁H₁₆NO₂: 194,1176 found: 194,1176 [α]_D²² -440,0° (c = 0.13 CHCl₃)

(S)-2-(N-methylformamido)-2-phenylethyl formate (89)



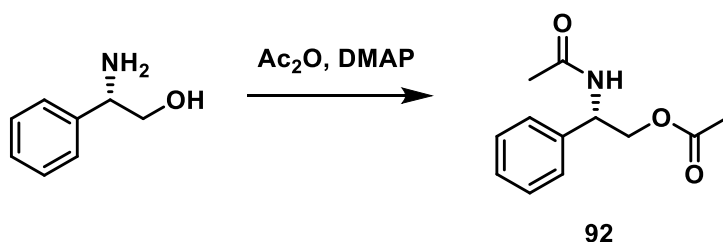
Following literature procedure.¹⁷³ HCOOH (150 μ L, 4 mmol, 4 eq.) solution in CHCl₃ (2 mL) was added dropwise while cooling into the DCC (412 mg, 2 mmol, 2 eq.) solution in CHCl₃ (3 mL). After 5 minutes, the white suspension was added dropwise into the solution of (S)-N-methyl-phenylglycinol (151 mg, 1 mmol, 1 eq.) in mixture of CHCl₃ (3 mL) and pyridine (1.5 mL) and stirred in ice bath for 16 hours. After 16 hours, the reaction mixture was evaporated, suspended in diethyl ether (10 mL) filtered and the filtrate was evaporated. The residue was then dissolved in ethyl acetate and extracted twice with 10% HCl and 10% K₂CO₃ and brine, dried with MgSO₄ and purified by column chromatography (Hexane: EtOAc 1:1) to yield 100 mg of oil (50%) as a mixture of two rotamers in approx. 10:6 ratio. Peaks belonging to major rotamer are designated M, peaks belonging to minor rotamer are designated m. ¹H NMR (500 MHz, CDCl₃) δ 8.31 (s, 1H, M), 8.18 (s, 1H, m), 8.10 (s, 1H, M), 8.08 (s, 1H, m), 7.43 – 7.31 (m, 5H, both rotamers), 7.29 – 7.22 (m, 5H, both rotamers), 5.91 (dd, *J* = 9.5, 5.3 Hz, 1H, m), 4.91 (dd, *J* = 10.0, 4.6 Hz, 1H, M), 4.79 – 4.72 (m, 1H, both rotamers), 4.67 – 4.62 (m, 1H, both rotamers), 2.76 (s, 3H, m), 2.69 (s, 3H, M). ¹³C NMR {¹H} (126 MHz, CDCl₃) δ 163.5 m, 163.1 M, 160.6 m, 160.4 M, 135.2 m, 134.8 M, 129.3, 129.1, 128.9, 128.6, 127.9, 127.2, 60.8 M, 59.6 m, 52.7 M, 49.3 m, 34.1, 30.6. HRMS (ESI) *m/z*: [M+H]⁺ calcd. for: C₁₁H₁₄NO₃: 208.0968 found: 208.0967 [α]_D²² +89.47 (c = 0.19 CHCl₃)

(S)-N-(2-hydroxy-1-phenylethyl)-N-methylformamide (90)



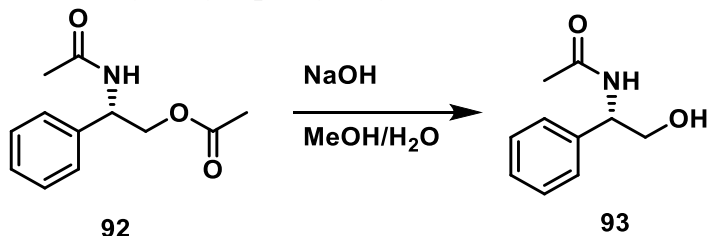
(S)-2-(N-methylformamido)-2-phenylethyl formate (80 mg, 0.38 mmol, 1 eq.) was dissolved in MeOH (8 mL) and NH_3 was added (25% aq. solution, 90 μL , 1.15 mmol, 3 eq) and the reaction was stirred at room temperature for 2 hours. After two hours, the solution was evaporated, dissolved in EtOAc, extracted with brine three times. Organic layer was separated, dried with MgSO_4 and evaporated. The residue was purified by column chromatography (EtOAc) to yield 21 mg (30%) of clear oil as a mixture of two rotamers in approx. 10:6 ratio. $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.33 (s, 1H, M), 8.21 (s, 1H, m), 7.40 – 7.22 (m, 10H, both rotamers), 5.41 (dd, $J = 8.4, 5.4$ Hz, 1H, m), 4.68 (dd, $J = 8.7, 5.3$ Hz, 1H, M), 4.17 – 4.08 (m, 4H, both rotamers), 2.80 (s, 3H, m), 2.70 (s, 3H, M). $^{13}\text{C NMR}$ $\{^1\text{H}\}$ (126 MHz, CDCl_3) δ 164.3, 163.9, 136.2, 136.1, 129.1, 129.0, 128.5, 128.3, 127.9, 127.4, 63.5, 61.6, 60.7, 58.7, 32.1, 26.6. **HRMS** (ESI) m/z : $[\text{M}+\text{H}]^+$ calcd. for: $\text{C}_{10}\text{H}_{14}\text{O}_2\text{N}_1$: 180.1019 found: 180.1019, $[\alpha]_d^{22} +41.51$ ($c = 0.21$ CHCl_3)

(S)-2-acetamido-2-phenylethyl acetate (92)



(S)-phenylglycinol (670 mg, 5 mmol, 1 eq.) and DMAP (70 mg, 0.5 mmol, 0.1 eq.) was dissolved in Ac_2O (7 mL) and stirred at room temperature for 2.5 hr. After 2.5 hours, the solution was added dropwise into 10% K_2CO_3 aq. solution (15 mL). The solution was further neutralized with solid K_2CO_3 until $\text{pH} = 7$ and then extracted into DCM (3×30 mL). Organic layers were combined and dried with MgSO_4 and evaporated to yield white solid (573 mg, 50%) $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.37 – 7.33 (m, 2H), 7.31 – 7.27 (m, 3H), 6.09 (d, $J = 6.4$ Hz, 1H), 5.29 (td, $J = 7.6, 4.7$ Hz, 1H), 4.43 (dd, $J = 11.5, 7.2$ Hz, 1H), 4.26 (dd, $J = 11.5, 4.7$ Hz, 1H), 2.05 (s, 3H), 2.02 (s, 3H). $^{13}\text{C NMR}$ $\{^1\text{H}\}$ (126 MHz, CDCl_3) δ 171.4, 169.7, 138.5, 129.0, 128.1, 126.8, 66.2, 52.7, 23.5, 21.0. **HRMS** (ESI) m/z : $[\text{M}+\text{H}]^+$ calcd. for: $\text{C}_{12}\text{H}_{16}\text{NO}_3$: 222.1130 found: 222.1125 $[\alpha]_d^{22} +80,77^\circ$ ($c = 0.13$ CHCl_3)

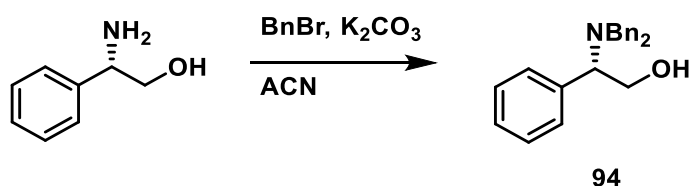
(S)-N-(2-hydroxy-1-phenylethyl)acetamide (93)



(S)-2-acetamido-2-phenylethyl acetate 300 mg, 1.35 mmol, 1 eq.) was dissolved in MeOH (15 mL) and NaOH solution (270 mg, 6.75 mmol, 5eq. dissolved in 5 mL of DI water) and stirred at room temperature for 12 hours. After 12 hours, the mixture was filtered through pad of celite, washed with 30 mL of EtOAc: MeOH (1:1) and the filtrate was dried with MgSO_4 and evaporated yielding white solid (228 mg, 93%) $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.37 – 7.33 (m, 2H), 7.31 – 7.27 (m, 3H), 6.38 (d, $J = 3.5$ Hz,

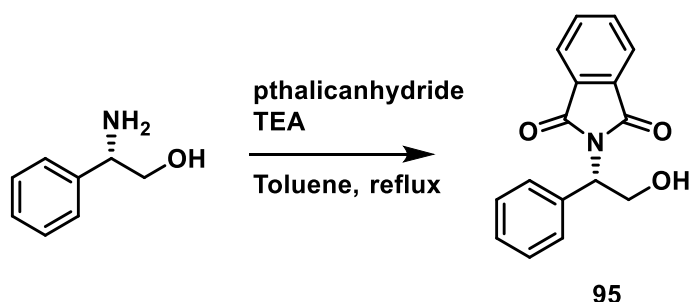
1H), 5.04 (dt, $J = 7.1, 5.1$ Hz, 1H), 3.85 (d, $J = 5.1$ Hz, 2H), 3.12 (s, 1H), 2.02 (s, 3H). $^{13}\text{C NMR}$ $\{^1\text{H}\}$ (126 MHz, CDCl_3) δ 171.0, 139.1, 129.0, 128.0, 126.9, 66.6, 56.1, 23.4. **HRMS** (ESI) m/z : $[\text{M}+\text{H}]^+$ calcd. for: $\text{C}_{10}\text{H}_{14}\text{NO}_2$: 180.1019 found: 180.1019 $[\alpha]_d^{22} +45.26^\circ$ ($c = 0.19$ CHCl_3)

(S)-2-(dibenzylamino)-2-phenylethan-1-ol (94)



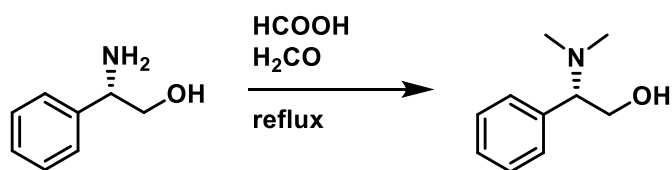
Following literature procedure.¹⁷⁵ (*S*)-phenylglycinol (137 mg, 1 mmol, 1 eq.) was dissolved in acetonitrile (7 mL), K_2CO_3 (280 mg, 2 mmol, 2 eq.) was added followed by benzyl bromide (250 μL , 2.1 mmol, 2.1 eq.). The reaction was stirred at 60°C for 24 hrs. After the reaction was complete (TLC Hexane: EtOAc 4:1), the reaction was filtered and the filtrate was evaporated and purified by column chromatography (Hexane: EtOAc, gradient from 10:1 to 8:1). Isolated as a colorless oil (199 mg, 62%) $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.48 – 7.34 (m, 3H), 7.34 (d, $J = 4.4$ Hz, 8H), 7.27 (q, $J = 3.9, 3.2$ Hz, 4H), 4.14 (t, $J = 10.6$ Hz, 1H), 3.96 – 3.93 (m, 1H), 3.62 (dd, $J = 10.8, 5.2$ Hz, 1H), 3.16 (d, $J = 13.4$ Hz, 1H). $^{13}\text{C NMR}$ $\{^1\text{H}\}$ (101 MHz, CDCl_3) δ 139.3, 135.3, 129.4, 129.1, 128.7, 128.5, 128.2, 127.4, 63.2, 60.6, 53.7. **HRMS** (ESI- TOF) m/z : $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}$: 318.1852; found: 318.1853, $[\alpha]_d^{22} +122.33^\circ$ ($c = 0.6$, CHCl_3)

(S)-2-(2-hydroxy-1-phenylethyl)isoindoline-1,3-dione (95)



Following literature procedure.¹⁷⁶ (*S*)-phenylglycinol (420 mg, 3 mmol, 1 eq.) was suspended in toluene (10 mL), phthalic anhydride (450 mg, 3 mmol, 1 eq.) was added, followed by triethylamine (50 μL , 0.3 mmol, 0.1 eq.). Reaction was refluxed for 16 hrs. The reaction was then cooled to the room temperature, evaporated and the residue was dissolved in EtOAc (25 mL) and extracted with 10% aq. HCl (3×25 mL) and 10% aq. K_2CO_3 (3×25 mL). Combined organic layers were washed with brine, dried with MgSO_4 and evaporated. The residue was purified by column chromatography (Hexane: EtOAc 2:1). 390mg (50%). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.83 (dd, $J = 5.6, 3.2$ Hz, 2H), 7.71 (td, $J = 5.3, 2.1$ Hz, 2H), 7.46 (dd, $J = 6.9, 1.5$ Hz, 2H), 7.39 – 7.23 (m, 3H), 5.47 (dd, $J = 9.0, 5.0$ Hz, 1H), 4.65 (dd, $J = 11.7, 8.9$ Hz, 1H), 4.24 (dd, $J = 11.7, 5.0$ Hz, 1H). $^{13}\text{C NMR}$ $\{^1\text{H}\}$ (101 MHz, CDCl_3) δ 169.0, 137.0, 134.3, 132.0, 128.9, 128.3, 128.0, 123.6, 62.5, 57.7. **HRMS** (ESI- TOF) m/z : $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_3$: 268.0968; found: 268.0967, $[\alpha]_d^{22} -45.17^\circ$ ($c = 0.29$, CHCl_3)

(S)-2-(dimethylamino)-2-phenylethan-1-ol



Following literature procedure.²⁰⁶ (S)-phenylglycinol (550 mg, 4 mmol, 1 eq.) was dissolved in HCOOH (0.6 mL) and formaldehyde was added (38% aq. solution, 0.6 mL) and the reaction was heated at 90°C for 16 hours. After 16 hrs. the solution was cooled to room temperature, basified with NH₃ solution (25% aq. solution, 0.5 mL) and extracted 3 times with DCM. The organic phases were combined and dried with MgSO₄, evaporated and purified by column chromatography (EtOAc: MeOH 20:1) yielding 400 mg (60%) of brown oil which solidified by standing at room temperature. ¹H NMR (400 MHz, CDCl₃) δ 7.41 – 7.28 (m, 3H), 7.25 – 7.16 (m, 2H), 3.93 (dd, *J* = 10.7, 9.0 Hz, 1H), 3.68 (dd, *J* = 10.6, 5.3 Hz, 1H), 3.57 (dd, *J* = 9.0, 5.3 Hz, 1H), 2.21 (s, 3H). ¹³C NMR {¹H} (101 MHz, CDCl₃) δ 135.9, 129.1, 128.3, 128.0, 70.3, 61.4, 41.5. HRMS (ESI) *m/z*: [M+H]⁺ calcd. for: C₁₀H₁₆NO: 166.1266 found: 166.1266 [α]_d²²+32.5° (c= 0.36 CHCl₃)

Compounds **96-103** were prepared by following the general procedure for TBBA ester formation

P-(S)-2-((tert-butoxycarbonyl)(methyl)amino)-2-phenylethyl benzo[d]imidazol-1-yl)benzoate (*P*)-96

Purified by CC (Hexane: EtOAc 5:1), Yield: 19 mg (70%) ¹H NMR (400 MHz, CDCl₃) δ 8.21 (d, *J* = 6.3 Hz, 1H), 7.99 – 7.91 (m, 1H), 7.77 (t, *J* = 7.5 Hz, 1H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.42 – 7.33 (m, 2H), 7.32 – 7.23 (m, 3H), 7.10 (br.s, 2H), 7.00 – 6.97 (m, 1H), 5.42 (d, *J* = 197.9 Hz, 1H), 4.46 (s, 2H), 2.51 (s, 3H), 1.41 (s, 9H). ¹³C NMR {¹H} (126 MHz, CDCl₃) δ 163.5, 141.09 (q, *J* = 38.6 Hz), 140.8, 137.6, 136.8, 134.5, 133.8, 132.6, 130.6, 130.2, 128.8, 128.6, 127.9, 127.3, 127.0, 126.0, 124.0, 121.7, 119.0 (q, *J* = 273.3 Hz), 110.8, 80.2, 62.8, 55.4, 29.8, 28.5. ¹⁹F NMR (471 MHz, CDCl₃) δ -61.4. HRMS (ESI) *m/z*: [M + H]⁺ calcd. For C₂₉H₂₉N₃O₄F₃; 540.2105; found: 540.2109. [α]_d²² -10.53° (c= 0.095 CHCl₃) ¹H NMR (400 MHz, Acetone-D₆) δ 8.24 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.99 – 7.92 (m, 1H), 7.90 – 7.85 (m, 1H), 7.83 (t, *J* = 7.4 Hz, 1H), 7.75 (d, *J* = 7.9 Hz, 1H), 7.45 – 7.38 (m, 2H), 7.34 (tt, *J* = 8.1, 1.9 Hz, 2H), 7.30 – 7.25 (m, 1H), 7.23 (d, *J* = 7.1 Hz, 2H), 7.08 – 7.03 (m, 1H), 5.47 (d, *J* = 109.5 Hz, 1H), 4.51 (s, 2H), 2.58 (s, 3H), 1.40 (s, 9H). ¹H NMR (400 MHz, CDCl₃+TFAOMe) δ 8.18 (d, *J* = 7.7 Hz, 1H), 7.94 – 7.88 (m, 1H), 7.75 (t, *J* = 7.6 Hz, 1H), 7.65 (t, *J* = 7.6 Hz, 1H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.40 – 7.30 (m, 2H), 7.28 – 7.20 (m, 4H), 7.07 (d, *J* = 4.2 Hz, 2H), 6.95 (d, *J* = 8.2 Hz, 1H), 5.39 (d, *J* = 194.0 Hz, 1H), 4.51 – 4.24 (m, 2H), 2.49 (s, 3H), 1.37 (s, 9H).

M-(S)-2-((tert-butoxycarbonyl)(methyl)amino)-2-phenylethyl benzo[d]imidazol-1-yl)benzoate (*M*)-96

Purified by CC (Hexane: EtOAc 5:1), Yield: 22 mg (81%) ¹H NMR (500 MHz, CDCl₃) δ 8.21 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.93 (d, *J* = 7.7 Hz, 1H), 7.77 (t, *J* = 7.5 Hz, 1H), 7.68 (s, 1H), 7.49 (d, *J* = 7.8 Hz, 1H), 7.40 – 7.33 (m, 2H), 7.31 – 7.22 (m, 3H), 7.09 (d, *J* = 30.8 Hz, 2H), 6.96 (d, *J* = 8.2 Hz, 1H), 5.44 (d, *J* = 182.5 Hz, 1H), 4.50 (dd, *J* = 11.4, 5.6 Hz, 1H), 4.34 (d, *J* = 60.2 Hz, 1H), 2.42 (s, 3H), 1.41 (s, 9H). ¹³C NMR {¹H} (126 MHz, CDCl₃) δ 163.5, 155.8, 140.92 (q, *J* = 39.1 Hz), 140.8, 137.7, 136.9, 134.5, 133.9, 132.5, 130.6, 130.2, 128.8, 128.7, 127.9, 127.3, 127.0, 126.1, 124.0, 121.6, 119.00 (app. d, *J* = 271.9 Hz), 110.8, 80.2, 63.3, 56.9, 29.3, 28.5. ¹⁹F NMR (471 MHz, CDCl₃) δ -61.4. HRMS (ESI) *m/z*: [M + H]⁺ calcd. For C₂₉H₂₉N₃O₄F₃; 540.2105; found: 540.2108. [α]_d²² +12.27° (c= 0.22 CHCl₃) ¹H NMR (400 MHz, Acetone-D₆) δ 8.24 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.98 – 7.91 (m, 1H), 7.90 – 7.79 (m, 2H), 7.74 (d, *J* = 7.8 Hz, 1H), 7.43 – 7.36 (m, 2H), 7.35 – 7.24 (m, 3H), 7.20 (d, *J* = 7.0 Hz, 2H), 7.01 (d, *J* = 8.2 Hz, 1H), 5.44 (d, *J* = 103.3 Hz, 1H), 4.52 (dd, *J* = 11.5, 5.4 Hz, 1H), 4.45 (d, *J* = 9.8 Hz, 1H), 2.45 (s, 3H), 1.41 (s, 9H). ¹H NMR (400 MHz, CDCl₃+TFAOMe) δ 8.17 (d, *J* = 7.8 Hz, 1H), 7.89 (d, *J*

= 7.0 Hz, 1H), 7.74 (t, $J = 7.4$ Hz, 1H), 7.65 (t, $J = 7.7$ Hz, 1H), 7.46 (d, $J = 7.6$ Hz, 1H), 7.33 (p, $J = 7.2$ Hz, 2H), 7.28 – 7.18 (m, 3H), 7.03 (s, 2H), 6.92 (d, $J = 7.3$ Hz, 1H), 5.40 (d, $J = 139.4$ Hz, 1H), 4.51 – 4.20 (m, 2H), 2.38 (s, 3H), 1.37 (s, 9H).

***P*-(*S*)-2-(dimethylamino)-2-phenylethyl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (*P*)-97**

Purified by HPLC, Yield: 14 mg (50%) $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.06 (dd, $J = 7.8, 1.6$ Hz, 1H), 7.99 – 7.97 (m, 1H), 7.73 (td, $J = 7.7, 1.6$ Hz, 1H), 7.65 (td, $J = 7.7, 1.3$ Hz, 1H), 7.47 – 7.44 (m, 1H), 7.42 (ddd, $J = 8.2, 7.2, 1.2$ Hz, 1H), 7.36 (td, $J = 7.7, 7.2, 1.1$ Hz, 1H), 7.30 – 7.22 (m, 3H), 7.12 – 7.09 (m, 2H), 6.98 (dt, $J = 8.1, 0.9$ Hz, 1H), 4.29 (dd, $J = 11.5, 6.5$ Hz, 1H), 4.13 (dd, $J = 11.5, 6.1$ Hz, 1H), 2.98 (t, $J = 6.3$ Hz, 1H), 1.96 (s, 6H). $^{13}\text{C NMR}\{^1\text{H}\}$ (126 MHz, CDCl_3) δ 164.0, 141.1 (q, $J = 38.5$ Hz), 140.8, 137.8, 137.7, 134.0, 133.6, 132.5, 130.6, 130.0, 129.1, 128.4, 128.4, 127.8, 126.0, 124.0, 121.6, 118.9 (q, $J = 272.1$ Hz), 111.0, 68.3, 66.6, 42.7. $^{19}\text{F NMR}$ (471 MHz, CDCl_3) δ -61.3. **HRMS** (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd. For $\text{C}_{25}\text{H}_{23}\text{N}_3\text{O}_2\text{F}_3$: 454.1737; found: 454.1735. $[\alpha]_d^{22}$ -53.57° ($c = 0.14$, CHCl_3)

***M*-(*S*)-2-(dimethylamino)-2-phenylethyl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (*M*)-97**

Purified by HPLC, Yield: 14 mg (50%) $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.08 (dd, $J = 7.9, 1.6$ Hz, 1H), 7.96 (dt, $J = 8.2, 0.9$ Hz, 1H), 7.74 (td, $J = 7.7, 1.6$ Hz, 1H), 7.65 (td, $J = 7.7, 1.3$ Hz, 1H), 7.45 (dd, $J = 7.8, 0.9$ Hz, 1H), 7.40 (ddd, $J = 8.3, 7.2, 1.1$ Hz, 1H), 7.33 (ddd, $J = 8.2, 7.2, 1.1$ Hz, 1H), 7.27 – 7.21 (m, 3H), 7.04 – 7.00 (m, 2H), 6.94 (dt, $J = 8.2, 1.0$ Hz, 1H), 4.34 (dd, $J = 11.5, 6.6$ Hz, 1H), 4.14 (dd, $J = 11.5, 5.9$ Hz, 1H), 3.09 (t, $J = 6.2$ Hz, 1H), 2.06 (s, 6H). $^{13}\text{C NMR}\{^1\text{H}\}$ (126 MHz, CDCl_3) δ 164.0, 141.10 (q, $J = 38.5$ Hz), 140.8, 137.7, 137.5, 134.1, 133.6, 132.5, 130.6, 130.0, 129.1, 128.4, 127.8, 126.0, 124.0, 121.6, 119.0 (q, $J = 272.3$ Hz), 110.9, 68.4, 66.5, 42.8. $^{19}\text{F NMR}$ (471 MHz, CDCl_3) δ -61.3. **HRMS** (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd. For $\text{C}_{25}\text{H}_{23}\text{N}_3\text{O}_2\text{F}_3$: 454.1737; found: 454.1737. $[\alpha]_d^{22}$ +44.29° ($c = 0.14$, CHCl_3)

***P*-(*S*)-2-acetamido-2-phenylethyl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (*P*)-98**

Purified by CC, yield 5 mg (21%) $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.23 (ddd, $J = 7.8, 1.7, 0.3$ Hz, 1H), 7.94 (dt, $J = 8.2, 1.0$ Hz, 1H), 7.78 (td, $J = 7.7, 1.7$ Hz, 1H), 7.71 (td, $J = 7.7, 1.3$ Hz, 1H), 7.47 (dd, $J = 7.8, 1.2$ Hz, 1H), 7.41 (ddd, $J = 8.2, 7.2, 1.2$ Hz, 1H), 7.35 (ddd, $J = 8.3, 7.2, 1.1$ Hz, 1H), 7.20 – 7.17 (m, 3H), 6.96 – 6.94 (m, 1H), 6.92 – 6.89 (m, 2H), 5.58 (d, $J = 8.4$ Hz, 1H), 5.10 (ddd, $J = 8.2, 7.0, 4.0$ Hz, 1H), 4.39 (dd, $J = 11.7, 7.0$ Hz, 1H), 4.12 (dd, $J = 11.7, 4.0$ Hz, 1H), 1.99 (s, 3H). $^{13}\text{C NMR}\{^1\text{H}\}$ (126 MHz, CDCl_3) δ 169.8, 164.4, 141.25 (q, $J = 38.8, 38.8, 38.4$ Hz), 140.7, 134.1, 134.0, 133.1, 130.8, 130.1, 128.8, 128.4, 127.9, 126.4, 126.3, 124.4, 121.5, 118.9 (q, $J = 273.0$ Hz), 111.0, 67.4, 52.1, 23.3. $^{19}\text{F NMR}$ (376 MHz, CDCl_3) δ -61.67 **HRMS** (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd. For $\text{C}_{25}\text{H}_{21}\text{N}_3\text{O}_3\text{F}_3$: 468.1530; found: 468.1530. $[\alpha]_d^{22}$ +12.73° ($c = 0.05$, CHCl_3)

***M*-(*S*)-2-acetamido-2-phenylethyl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (*M*)-98**

Purified by CC, yield 10 mg (42%) $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.16 (dd, $J = 7.8, 1.6$ Hz, 1H), 7.95 (d, $J = 8.1$ Hz, 1H), 7.78 (td, $J = 7.7, 1.6$ Hz, 1H), 7.70 (td, $J = 7.7, 1.3$ Hz, 1H), 7.48 (d, $J = 7.1$ Hz, 1H), 7.42 (ddd, $J = 8.3, 7.3, 1.2$ Hz, 1H), 7.36 (td, $J = 7.7, 7.2, 1.1$ Hz, 1H), 7.31 – 7.25 (m, 4H), 7.13 – 7.10 (m, 2H), 6.98 – 6.96 (m, 1H), 5.56 (d, $J = 7.9$ Hz, 1H), 5.06 (d, $J = 11.9$ Hz, 1H), 4.46 (dd, $J = 11.7, 7.0$ Hz, 1H), 3.99 (dd, $J = 11.7, 4.2$ Hz, 1H), 1.86 (s, 3H). $^{13}\text{C NMR}\{^1\text{H}\}$ (126 MHz, CDCl_3) δ 169.7, 164.4, 141.2 (app. d, $J = 38.6$ Hz), 140.8, 137.7, 134.1, 134.1, 132.7, 130.8, 130.2, 128.9, 128.4, 128.1, 126.6, 126.2, 124.2, 121.8, 118.9 (q, $J = 271.9$ Hz), 110.8, 67.1, 52.4, 23.3. $^{19}\text{F NMR}$ (376 MHz, CDCl_3) δ -61.89 **HRMS** (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd. For $\text{C}_{25}\text{H}_{21}\text{N}_3\text{O}_3\text{F}_3$: 468.1530; found: 468.1532. $[\alpha]_d^{22}$ +60.0° ($c = 0.1$, CHCl_3)

***P*-(*S*)-2-(*N*-methylacetamido)-2-phenylethyl 2-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-1-yl)benzoate (*P*)-99**

Purified by CC (Hexane: EtOAc 1:1), yield 17 mg (70%) ¹H NMR (500 MHz, CDCl₃) δ 8.19 (dd, *J* = 7.9, 1.5 Hz, 1H, both rotamers), 7.94 (d, *J* = 8.2 Hz, 1H, both rotamers), 7.77 (td, *J* = 7.7, 1.6 Hz, 1H, both rotamers), 7.70 (td, *J* = 7.7, 1.3 Hz, 1H, both rotamers), 7.49 (d, *J* = 8.0 Hz, 1H, both rotamers), 7.43 – 7.39 (m, 1H, both rotamers), 7.39 – 7.34 (m, 1H, both rotamers), 7.32 – 7.27 (m, 3H, both rotamers), 7.10 (dd, *J* = 7.3, 1.5 Hz, 1H, both rotamers), 7.05 – 7.01 (m, 1H, m), 7.00 – 6.97 (m, 1H, M), 6.09 (t, *J* = 7.5 Hz, 1H, M), 4.86 (dd, *J* = 8.8, 6.2 Hz, 1H, m), 4.55 (dd, *J* = 11.7, 6.0 Hz, 1H, m), 4.44 (d, *J* = 7.0 Hz, 2H, M), 4.29 (dd, *J* = 11.7, 8.9 Hz, 1H, m), 2.62 (s, 3H, m), 2.59 (s, 1H, M), 2.06 (s, 3H, M), 1.96 (s, 3H, m). ¹³C NMR{¹H} (126 MHz, CDCl₃) δ 171.6, 171.2, 163.8, 163.6, 141.03 (q, *J* = 38.5 Hz), 140.8, 137.6, 136.3, 135.7, 134.4, 134.3, 133.9, 132.5, 132.5, 130.9, 130.9, 130.4, 130.2, 129.2, 128.9, 128.5, 128.5, 128.2, 128.1, 127.6, 126.6, 126.6, 126.2, 126.1, 124.2, 124.1, 121.8, 121.6, 119.0 (d, *J* = 272.1 Hz), 110.9, 110.7, 63.8, 62.5, 58.6, 53.4, 30.8, 28.2, 22.2, 21.8. ¹⁹F NMR (471 MHz, CDCl₃) δ -61.36, -61.44. HRMS (ESI) *m/z*: [M + H]⁺ calcd. For C₂₆H₂₃N₃O₃F₃: 482.1686; found: 482.1685. [α]_D²² -392.36° (c = 0.17, CHCl₃)

***M*-(*S*)-2-(*N*-methylacetamido)-2-phenylethyl 2-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-1-yl)benzoate (*M*)-99**

Purified by CC (Hexane: EtOAc 1:1), yield 12 mg (50%) ¹H NMR (500 MHz, CDCl₃) δ 8.19 (dd, *J* = 7.8, 1.6 Hz, 1H, M), 8.16 (dd, *J* = 7.9, 1.6 Hz, 1H, m), 8.00 – 7.91 (m, 1H, M), 7.92 (dt, *J* = 8.2, 1.0 Hz, 1H, m), 7.81 (td, *J* = 7.7, 1.6 Hz, 1H, m), 7.77 (td, *J* = 7.7, 1.6 Hz, 1H, M), 7.73 (td, *J* = 7.7, 1.3 Hz, 1H, m), 7.69 (td, *J* = 7.7, 1.3 Hz, 1H, M), 7.52 (dd, *J* = 7.9, 1.2 Hz, 1H, m), 7.48 (dd, *J* = 7.7, 1.3 Hz, 1H, M), 7.43 – 7.24 (m, 10H, both rotamers), 7.15 – 7.06 (m, 2H, M), 7.00 (ddd, *J* = 7.9, 1.6, 0.8 Hz, 1H, m), 6.99 – 6.97 (m, 1H, M), 6.95 (dt, *J* = 8.0, 1.1 Hz, 1H, m), 6.02 (dd, *J* = 9.2, 5.5 Hz, 1H, M), 4.97 (dd, *J* = 9.2, 5.7 Hz, 1H, m), 4.55 (dd, *J* = 11.5, 5.5 Hz, 1H, M), 4.49 (dd, *J* = 11.7, 5.7 Hz, 1H, m), 4.40 (dd, *J* = 11.5, 9.2 Hz, 1H, M), 4.28 (dd, *J* = 11.7, 9.3 Hz, 1H, m), 2.51 (s, 3H, m), 2.42 (s, 3H, M), 2.13 (s, 2H, m), 1.97 (s, 3H, M). ¹³C NMR{¹H} (126 MHz, CDCl₃) δ 171.3, 171.3, 163.8, 163.6, 141.20 (d, *J* = 38.3 Hz), 140.9, 140.7, 136.4, 135.7, 134.4, 134.3, 133.9, 132.7, 132.3, 130.9, 130.8, 130.1, 129.1, 128.9, 128.5, 128.4, 128.1, 127.6, 126.6, 126.3, 125.9, 124.2, 124.0, 121.7, 121.5, 118.97 (q, *J* = 272.5 Hz), 110.8, 63.7, 62.9, 58.6, 53.8, 31.0, 28.0, 22.3, 21.7. ¹⁹F NMR (471 MHz, CDCl₃) δ -61.4, -61.5. HRMS (ESI) *m/z*: [M + H]⁺ calcd. For C₂₆H₂₃N₃O₃F₃: 482.1686; found: 482.1685. [α]_D²² +127.5° (c = 0.12, CHCl₃)

***P*-(*S*)-2-(*N*-methylformamido)-2-phenylethyl 2-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-1-yl)benzoate (*P*)-100**

Purified by CC (Hexane: EtOAc 2:1), yield 18 mg (78%) ¹H NMR (500 MHz, CDCl₃) δ 8.20 (dt, *J* = 7.8, 1.9 Hz, 1H, both rotamers), 8.08 (s, 1H, m), 7.98 – 7.96 (m, 1H, M), 7.95 (dt, *J* = 8.2, 0.9 Hz, 1H, m), 7.81 (td, *J* = 7.7, 1.6 Hz, 1H, M), 7.77 (td, *J* = 7.6, 1.7 Hz, 1H, m), 7.75 – 7.72 (m, 1H, M), 7.72 – 7.69 (m, 1H, m), 7.54 (s, 1H, M), 7.52 (dd, *J* = 7.8, 1.2 Hz, 1H, M), 7.48 (dd, *J* = 7.9, 1.4 Hz, 1H, m), 7.47 – 7.44 (m, 2H, M), 7.43 – 7.36 (m, 2H, m), 7.35 – 7.27 (m, 5H, both rotamers), 7.17 – 7.08 (m, 1H, M), 7.06 – 6.96 (m, 1H, both rotamers), 6.98 (dd, *J* = 1.4, 0.7 Hz, 1H, m), 5.77 (dd, *J* = 10.0, 5.3 Hz, 1H, m), 4.60 (dd, *J* = 11.7, 10.0 Hz, 1H, M), 4.53 – 4.43 (m, 2H, m), 4.28 (dd, *J* = 11.7, 4.7 Hz, 1H, M), 4.15 (dd, *J* = 10.0, 4.6 Hz, 1H, M), 2.56 (s, 3H, m), 2.51 (s, 3H, M). ¹³C NMR{¹H} (126 MHz, CDCl₃) δ 163.8, 163.6, 163.5, 162.8, 141.26 (q, *J* = 34.0), 140.8, 140.7, 137.8, 137.6, 135.0, 134.6, 134.3, 134.2, 134.0, 132.8, 132.6, 130.9, 130.9, 130.2, 130.2, 129.2, 129.0, 128.8, 128.5, 128.4, 128.2, 127.7, 127.0, 126.4, 126.1, 124.3, 124.1, 121.6, 118.9 (q, *J* = 271.8 Hz), 111.0, 110.9, 62.4, 61.8, 59.4, 52.6, 30.1, 25.9. ¹⁹F NMR (471 MHz, CDCl₃) δ -61.3, -61.5. HRMS (ESI) *m/z*: [M + H]⁺ calcd. For C₂₅H₂₁N₃O₃F₃: 468.1530; found: 468.1531. [α]_D²² +23.33° (c = 0.18, CHCl₃)

***M*-(*S*)-2-(*N*-methylformamido)-2-phenylethyl 2-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-1-yl)benzoate (*M*)-100**

Purified by CC (Hexane: EtOAc 2:1), yield 16 mg (70%) $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.29 – 8.21 (m, 1H, m), 8.17 (s, 1H, m), 8.21 – 8.12 (m, 1H, m), 7.97 – 7.94 (m, 1H, m), 7.94 – 7.92 (m, 1H, M), 7.81 (td, $J = 7.7$, 1.6 Hz, 1H, M), 7.77 (td, $J = 7.7$, 1.7 Hz, 1H, m), 7.73 (dd, $J = 7.8$, 1.3 Hz, 1H, M), 7.75 – 7.66 (m, 2H, m), 7.52 (dd, $J = 7.8$, 1.1 Hz, 1H, M), 7.47 (dd, $J = 7.8$, 1.3 Hz, 1H, m), 7.44 – 7.27 (m, 10H, both rotamers), 7.10 (m, 2H, m), 7.05 (dd, m, 2H, M), 7.01 (ddd, $J = 7.8$, 1.4, 0.7 Hz, 1H, m), 6.98 (d, m, 1H, M), 5.71 (dd, $J = 10.4$, 4.8 Hz, 1H, m), 4.68 – 4.55 (m, 1H, M), 4.61 – 4.58 (m, 1H, m), 4.43 (dd, $J = 9.8$, 1.7 Hz, 1H, m), 4.43 (ddd, $J = 11.6$, 10.2, 8.2 Hz, 1H, m), 4.33 (dd, $J = 7.1$, 4.7 Hz, 1H, M), 2.43 (s, 3H, M), 2.25 (s, 3H, m). $^{13}\text{C NMR}\{^1\text{H}\}$ (126 MHz, CDCl_3) δ 163.7, 163.7, 163.3, 162.8, 141.32 (app. d, $J = 38.5$ Hz), 140.9, 140.7, 137.7, 135.0, 134.7, 134.4, 134.3, 134.2, 134.0, 133.0, 132.4, 130.9, 130.9, 130.3, 130.1, 129.2, 129.0, 128.8, 128.5, 128.4, 128.2, 127.7, 127.0, 126.3, 126.0, 124.2, 124.0, 121.6, 121.5, 118.97 (q, $J = 272.0$ Hz), 111.1, 110.9, 62.5, 61.8, 59.4, 52.5, 29.8, 26.0. $^{19}\text{F NMR}$ (471 MHz, CDCl_3) δ -61.4, -61.5. **HRMS** (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd. For $\text{C}_{25}\text{H}_{21}\text{N}_3\text{O}_3\text{F}_3$: 468.1530; found: 468.1531. $[\alpha]_D^{22} +67.50^\circ$ ($c = 0.16$, CHCl_3)

***P*-(*S*)-2-amino-2-phenylethyl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (*P*)-101**

Compound (*P*)-77 (15 mg, 0.028 mmol) was dissolved in dry DCM (2 mL) and TFA (250 μL) was added. Reaction was stirred at room temperature for 20 minutes. The solution was evaporated by stream of nitrogen, dissolved in EtOAc (2 mL) and extracted with sat. NaHCO_3 . Organic layer was dried with MgSO_4 and evaporated to yield 8.5 mg of oil (70%) $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.28 – 8.25 (m, 1H), 8.01 – 7.98 (m, 1H), 7.79 (td, $J = 7.6$, 1.7 Hz, 1H), 7.73 (td, $J = 7.7$, 1.3 Hz, 1H), 7.51 (dd, $J = 7.8$, 1.2 Hz, 1H), 7.45 – 7.38 (m, 2H), 7.29 – 7.20 (m, 3H), 7.19 – 7.17 (m, 2H), 7.07 – 7.05 (m, 1H), 3.97 – 3.83 (m, 2H), 3.55 (dd, $J = 9.0$, 3.9 Hz, 1H), 1.07 (br.s, 2H). $^{13}\text{C NMR}\{^1\text{H}\}$ (126 MHz, CDCl_3) δ 164.3, 141.31 (app. d, $J = 38.7$ Hz), 140.8, 137.9, 133.9, 133.8, 133.1, 130.8, 130.1, 129.2, 128.7, 127.9, 126.8, 126.3, 124.3, 121.7, 119.0 (q, $J = 272.0$ Hz), 111.0, 71.6, 54.2. $^{19}\text{F NMR}$ (471 MHz, CDCl_3) δ -61.5. **HRMS** (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd. For $\text{C}_{23}\text{H}_{19}\text{N}_3\text{O}_2\text{F}_3$: 426.1424; found: 426.1424. $[\alpha]_D^{22} +70.59^\circ$ ($c = 0.09$, CHCl_3)

***M*-(*S*)-2-amino-2-phenylethyl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (*M*)-101**

Compound (*M*)-77 (21 mg, 0.04 mmol) was dissolved in dry DCM (2 mL) and TFA (250 μL) was added. Reaction was stirred at room temperature for 20 minutes. The solution was evaporated by stream of nitrogen, dissolved in EtOAc (2 mL) and extracted with sat. NaHCO_3 . Organic layer was dried with MgSO_4 and evaporated to yield 10 mg of oil (58%) $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.22 (dd, $J = 7.8$, 1.6 Hz, 1H), 8.00 – 7.98 (m, 1H), 7.79 (td, $J = 7.7$, 1.6 Hz, 1H), 7.72 (td, $J = 7.7$, 1.3 Hz, 1H), 7.51 (d, $J = 7.7$ Hz, 1H), 7.44 (ddd, $J = 8.2$, 7.3, 1.1 Hz, 1H), 7.38 (td, $J = 7.8$, 7.3, 1.1 Hz, 1H), 7.28 – 7.20 (m, 3H), 7.14 – 7.11 (m, 2H), 7.03 – 7.00 (m, 1H), 3.94 – 3.89 (m, 1H), 3.86 (dd, $J = 10.9$, 8.9 Hz, 1H), 3.57 (dd, $J = 8.7$, 4.0 Hz, 1H), 1.36 (br.s, 2H). $^{13}\text{C NMR}\{^1\text{H}\}$ (126 MHz, CDCl_3) δ 164.4, 141.21 (q, $J = 38.1$ Hz), 140.8, 137.8, 133.8, 132.8, 130.7, 130.1, 129.2, 128.7, 127.9, 126.7, 126.2, 124.3, 121.7, 119.00 (q, $J = 272.1$ Hz), 110.9, 71.6, 54.2. $^{19}\text{F NMR}$ (471 MHz, CDCl_3) δ -61.2. **HRMS** (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd. For $\text{C}_{23}\text{H}_{19}\text{N}_3\text{O}_2\text{F}_3$: 426.1424; found: 426.1422. $[\alpha]_D^{22} +48.0^\circ$ ($c = 0.1$, CHCl_3)

***P*-(*S*)-2-(dibenzylamino)-2-phenylethyl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (*P*)-102**

Purified by column chromatography (Hexane: EtOAc 6:1) 12 mg (40%) $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.05 (dd, $J = 7.8$, 1.4 Hz, 1H), 7.86 (d, $J = 8.1$ Hz, 1H), 7.75 (td, $J = 7.7$, 1.6 Hz, 1H), 7.65 (td, $J = 7.7$, 1.3 Hz, 1H), 7.46 – 7.44 (m, 2H), 7.35 – 7.31 (m, 3H), 7.31 – 7.26 (m, 9H), 7.23 (ddd, $J = 12.0$, 7.3, 2.2 Hz, 3H), 7.13 (d, $J = 6.9$ Hz, 2H), 6.87 (dt, $J = 8.2$, 0.9 Hz, 1H), 4.53 (dd, $J = 11.4$, 6.7 Hz, 1H), 4.33 (dd, $J = 11.4$, 7.4 Hz, 1H), 3.78 (t, $J = 7.0$ Hz, 1H), 3.66 (d, $J = 13.8$ Hz, 2H), 3.23 (d, $J = 13.8$ Hz, 2H). $^{13}\text{C NMR}\{^1\text{H}\}$ (126 MHz, CDCl_3) δ 163.8, 140.95 (q, $J = 38.5$ Hz), 140.7, 139.7, 137.6, 136.5, 134.3, 133.6, 132.3, 130.5, 130.2, 129.0, 128.9, 128.7, 128.4, 128.3, 127.7, 127.1, 125.9, 123.9, 121.6, 118.9 (q, $J = 272.0$ Hz), 110.7, 64.3, 60.4, 54.2. $^{19}\text{F NMR}$ (471 MHz, CDCl_3) δ -61.3. **HRMS** (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd. For $\text{C}_{37}\text{H}_{31}\text{N}_3\text{O}_2\text{F}_3$: 606.2363; found: 606.2364. $[\alpha]_D^{22} +11.67^\circ$ ($c = 0.12$, CHCl_3)

***M*-(*S*)-2-(dibenzylamino)-2-phenylethyl
yl)benzoate (*M*)-102**

2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (*M*)-102

Purified by column chromatography (Hexane: EtOAc 6:1) 14 mg (46%) $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.04 (dd, $J = 7.9, 1.6$ Hz, 1H), 7.87 (d, $J = 8.2$ Hz, 1H), 7.74 (td, $J = 7.7, 1.6$ Hz, 1H), 7.65 (td, $J = 7.7, 1.3$ Hz, 1H), 7.47 – 7.44 (m, 2H), 7.37 – 7.31 (m, 2H), 7.31 – 7.26 (m, 10H), 7.23 (ddd, $J = 13.0, 5.0, 2.8$ Hz, 4H), 7.10 (d, $J = 7.1$ Hz, 2H), 6.89 (dt, $J = 8.2, 0.9$ Hz, 1H), 4.51 (dd, $J = 11.4, 6.7$ Hz, 1H), 4.42 (dd, $J = 11.4, 7.5$ Hz, 1H), 3.88 (t, $J = 7.0$ Hz, 1H), 3.65 (d, $J = 13.8$ Hz, 2H), 3.27 (d, $J = 13.8$ Hz, 2H). $^{13}\text{C NMR}\{^1\text{H}\}$ (126 MHz, CDCl_3) δ 163.7, 141.03 (q, $J = 38.3$ Hz), 140.8, 139.7, 137.6, 136.5, 134.4, 133.6, 132.3, 130.5, 130.1, 128.9, 128.8, 128.7, 128.4, 128.3, 127.7, 127.1, 125.9, 123.9, 121.6, 119.0 (q, $J = 272.0$ Hz), 110.7, 64.1, 60.3, 54.2. $^{19}\text{F NMR}$ (471 MHz, CDCl_3) δ -61.4. **HRMS** (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd. For $\text{C}_{37}\text{H}_{31}\text{N}_3\text{O}_2\text{F}_3$: 606.2363; found: 606.2365. $[\alpha]_D^{22} +72.86^\circ$ ($c = 0.14$, CHCl_3)

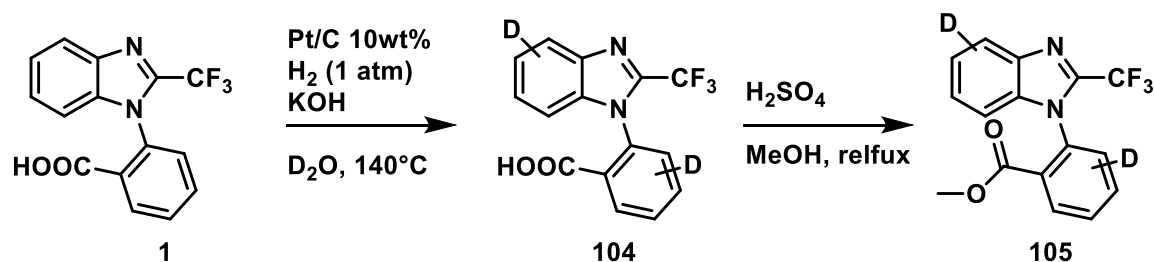
***P*-(*S*)-2-(1,3-dioxoisindolin-2-yl)-2-phenylethyl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (*P*)-103**

Purified by column chromatography (Hexane: EtOAc 2:1) 13 mg (46%) $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.09 (dd, $J = 7.9, 1.6$ Hz, 1H), 7.87 (d, $J = 8.1$ Hz, 1H), 7.81 (dd, $J = 5.5, 3.0$ Hz, 2H), 7.74 – 7.72 (m, 1H), 7.77 – 7.67 (m, 2H), 7.63 (td, $J = 7.7, 1.1$ Hz, 1H), 7.42 (d, $J = 7.7$ Hz, 1H), 7.37 – 7.33 (m, 3H), 7.31 – 7.24 (m, 4H), 6.92 (d, $J = 8.2$ Hz, 1H), 5.32 (dd, $J = 9.8, 5.5$ Hz, 1H), 4.94 (dd, $J = 11.4, 9.8$ Hz, 1H), 4.72 (dd, $J = 11.5, 5.5$ Hz, 1H). $^{13}\text{C NMR}\{^1\text{H}\}$ (126 MHz, CDCl_3) δ 167.9, 163.7, 140.85 (q, $J = 38.4$ Hz), 140.7, 134.2, 134.2, 133.8, 132.5, 131.9, 130.6, 130.2, 128.6, 128.1, 126.0, 124.0, 123.5, 121.7, 118.8 (q, $J = 273.0$ Hz), 110.6, 63.6, 53.6. $^{19}\text{F NMR}$ (471 MHz, CDCl_3) δ -61.5. **HRMS** (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd. For $\text{C}_{31}\text{H}_{21}\text{N}_3\text{O}_4\text{F}_3$: 566.1479; found: 566.1481. $[\alpha]_D^{22} -49.26^\circ$ ($c = 0.13$, CHCl_3)

***M*-(*S*)-2-(1,3-dioxoisindolin-2-yl)-2-phenylethyl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (*M*)-103**

Purified by column chromatography (Hexane: EtOAc 2:1) 14 mg (49%) $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.11 (dd, $J = 7.9, 1.4$ Hz, 1H), 7.91 (dt, $J = 8.2, 0.8$ Hz, 1H), 7.82 – 7.78 (m, 2H), 7.75 – 7.72 (m, 1H), 7.72 – 7.70 (m, 2H), 7.63 (td, $J = 7.7, 1.3$ Hz, 1H), 7.43 (d, $J = 7.4$ Hz, 1H), 7.34 – 7.30 (m, 3H), 7.29 – 7.24 (m, 3H), 7.20 (ddd, $J = 8.2, 7.2, 1.0$ Hz, 1H), 6.87 (dt, $J = 8.2, 0.9$ Hz, 1H), 5.19 (dd, $J = 9.8, 5.5$ Hz, 1H), 5.02 (dd, $J = 11.4, 9.8$ Hz, 1H), 4.62 (dd, $J = 11.5, 5.5$ Hz, 1H). $^{13}\text{C NMR}\{^1\text{H}\}$ (126 MHz, CDCl_3) δ 167.9, 163.7, 140.95 (q, $J = 38.8$ Hz), 140.7, 137.6, 136.0, 134.2, 134.2, 133.9, 132.6, 131.9, 130.6, 130.2, 128.9, 128.6, 128.6, 128.0, 125.9, 123.9, 123.5, 121.8, 118.88 (q, $J = 271.5$ Hz), 110.5, 63.8, 53.6. $^{19}\text{F NMR}$ (471 MHz, CDCl_3) δ -61.4. **HRMS** (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd. For $\text{C}_{31}\text{H}_{21}\text{N}_3\text{O}_4\text{F}_3$: 566.1479; found: 566.1481. $[\alpha]_D^{22} +21.43^\circ$ ($c = 0.14$, CHCl_3)

2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoic acid-D (104)

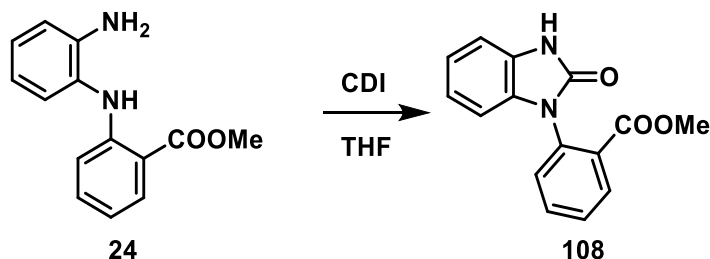


In an autoclave TBBA **1** (150 mg, 0.5 mmol, 1 eq) was suspended in D₂O (10 mL) and NaOH (20 mg, 0.5 mmol, 1 eq) was added and the mixture was stirred until dissolution. After dissolution, 10% Pt/C (100 mg, 0.05 mmol, 0.1 eq) and the autoclave was closed and purged three times with vacuum/argon. After final evacuation, H₂ (1 atm, 10 psi) was introduced. The reaction was heated for 24 hours to 160°C. **!!Careful: During the heating the internal pressure increased to 40 psi!!** After 24 hours, the reaction was cooled to room temperature, the Pt catalyst was removed by filtration through celite. The celite was washed with small amount 10% NaOH and the filtrate was acidified with conc. HCl (few drops) while cooling and stirring. Precipitated material was isolated by filtration (120 mg, 80%).

methyl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate-D (105)

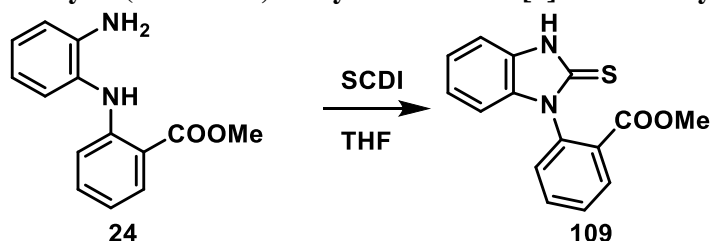
104 (120 mg, 0.4 mmol, 1 eq) was dissolved in MeOH (7.5 mL) and conc. H₂SO₄ (4 drops) was added. The mixture was refluxed for 16 hours. After 16 hours, reaction was cooled to room temperature and evaporated. The residue was dissolved in EtOAc (10 mL) and washed with K₂CO₃ (3x 10 mL), brine, dried with MgSO₄ and evaporated. Yield 100 mg (62%). ¹H NMR (400 MHz, CDCl₃) δ 8.22 (s, 0.8H), 7.50 (s, 0.11H), 7.39 (s, 0.14H), 7.02 – 6.93 (m, 0.75H), 3.45 (s, 3H).

methyl 2-(2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)benzoate (108)

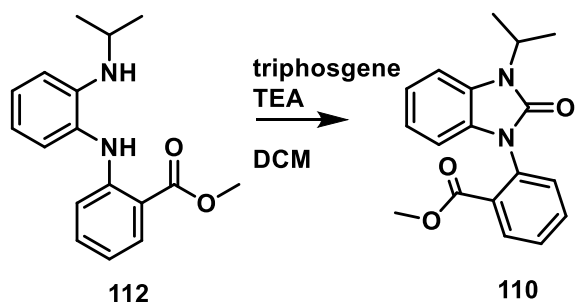


24 (1.6 g, 6.6 mmol, 1eq) was dissolved in THF, CDI (2.4 g, 13.2 mmol, 2 eq) was added and the mixture was stirred at room temperature for 18 hours. After 18 hours, 16 mL of 1M HCl was added slowly. The mixture was further diluted with water (60 mL) and extracted with EtOAc (3x60 mL), dried with MgSO₄ and evaporated. The residue was purified by column chromatography (Petroleum ether: EtOAc 3:1 → EtOAc). Yield 60% ¹H NMR (400 MHz, DMSO-*D*₆) δ 11.10 (s, 1H), 7.97 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.83 – 7.76 (m, 1H), 7.64 – 7.58 (m, 3H), 7.09 – 7.02 (m, 3H), 7.01 – 6.94 (m, 2H), 6.82 – 6.76 (m, 1H), 3.60 (s, 1H). ¹³C NMR {¹H} (101 MHz, DMSO-*D*₆) δ 166.1, 153.9, 134.0, 133.9, 131.5, 131.0, 129.2, 129.2, 129.0, 128.9, 122.2, 121.3, 109.7, 108.2, 52.7.

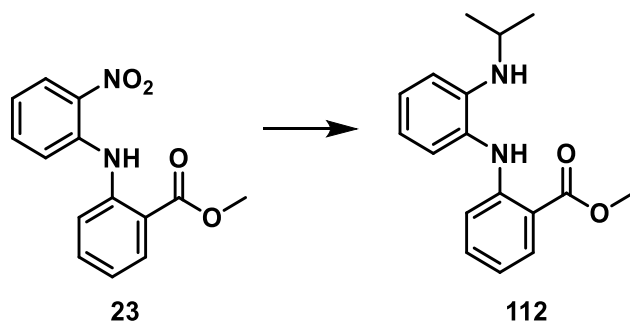
methyl 2-(2-thioxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)benzoate (109)



24 (242 mg, 1 mmol, 1 eq) was dissolved in THF (10 mL). Thiocarbonyldiimidazole (213 mg, 1.2 mmol, 1.2 eq) was added and the mixture was stirred at room temperature for 4 hours. After 4 hours, the reaction was quenched with 10% HCl (10 mL), water (20 mL) was added, and the solution was extracted with EtOAc (3x30 mL). Organic layers were combined, washed with brine, dried with MgSO₄ and evaporated to yield 253 mg (90%) of solid. ¹H NMR (400 MHz, DMSO-*D*₆) δ 8.06 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.85 (td, *J* = 7.7, 1.6 Hz, 1H), 7.70 (td, *J* = 7.7, 1.2 Hz, 1H), 7.56 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.28 – 7.19 (m, 3H), 7.12 (td, *J* = 7.7, 1.3 Hz, 1H), 6.76 (d, *J* = 7.9 Hz, 1H), 3.54 (s, 3H). ¹³C NMR {¹H} (101 MHz, DMSO-*D*₆) δ 169.5, 164.7, 134.7, 134.1, 133.8, 131.2, 131.2, 130.1, 129.6, 129.3, 123.2, 122.6, 109.7, 109.2, 52.3.

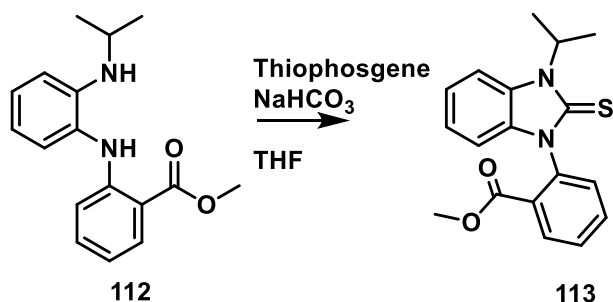
methyl 2-(3-isopropyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)benzoate (110)

112 (2020 mg, 7.11 mmol, 1 eq) was dissolved in dry DCM (35 mL) and trimethylamine (2.95 mL, 21.3 mmol, 3 eq) was added. Triphosgene (3200 mg, 10.6 mmol, 1.5 eq) was dissolved in DCM (35 mL) and slowly added into the solution of the starting material over 15 minutes. After the addition was complete, the reaction was stirred for 45 minutes. After 45 minutes, the reaction was washed with 10% HCl (3x 50 mL), water (3x 50 mL). Organic layer was dried with MgSO₄ and purified by column chromatography (hexane: EtOAc 3:1) to yield 1.5 g of oil (70%). ¹H NMR (400 MHz, DMSO-*D*₆) δ 7.98 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.81 (td, *J* = 7.8, 2.0 Hz, 1H), 7.62 (dt, *J* = 7.3, 3.4 Hz, 2H), 7.40 (d, *J* = 7.9 Hz, 1H), 7.11 (t, *J* = 7.7 Hz, 1H), 7.01 (t, *J* = 7.7 Hz, 1H), 6.83 (d, *J* = 7.4 Hz, 1H), 4.65 (hept, *J* = 7.0 Hz, 1H), 3.56 (s, 3H), 1.50 (dd, *J* = 6.9, 2.8 Hz, 6H). ¹³C NMR {¹H} (101 MHz, DMSO-*D*₆) δ 165.5, 152.1, 133.4, 131.1, 129.4, 128.8, 128.5, 128.3, 121.5, 120.8, 109.1, 107.8, 52.1, 44.6, 19.8, 19.7.

methyl 2-((2-(isopropylamino)phenyl)amino)benzoate (112)

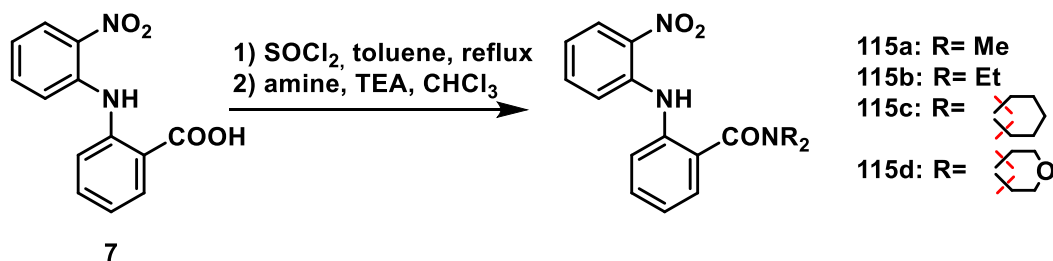
3-necked round-bottomed flask equipped with stir bar, valve and rubber septa was charged with 10% palladium on charcoal (200 mg, 5%). Methyl 2-((2-nitrophenyl)amino)benzoate **23** (1088 mg, 4 mmol, 1 eq) was dissolved in acetone (160 ml, 0.025 M) and glacial acetic acid was added (400 μL, 6.3 mmol, 1.6 eq). This solution was added to the flask, and it was closed with balloon. The system was evacuated and purged with nitrogen 4 times. After the last purge, the flask was evacuated and filled with hydrogen gas. The suspension was stirred overnight for 16 hours. After the reaction was complete, celite was added and the suspension was filtered. The solid was washed with approx. 100 ml of acetone and the combined organic layers were evaporated. The oily residue was purified by column chromatography (dry loading, column size: 10 x 3.5 cm, mobile phase: hexane: ethyl acetate 35:1, fraction size: 20 ml, product was collected in fractions 10-22) yielding 960 mg (85%) of yellow oil that solidified on air. ¹H NMR (400 MHz, DMSO-*D*₆) δ 8.72 (s, 1H), 7.87 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.31 (ddd, *J* = 8.6, 7.1, 1.7 Hz, 1H), 7.12 – 7.07 (m, 1H), 7.05 (dd, *J* = 7.7, 1.3 Hz, 1H), 6.75 (d, *J* = 7.3 Hz, 1H), 6.73 – 6.67 (m, 1H), 6.61 (td, *J* = 7.5, 1.3 Hz, 1H), 6.55 (dd, *J* = 8.5, 1.0 Hz, 1H), 4.42 (d, *J* = 8.4 Hz, 1H), 3.86 (s, 3H), 3.68 – 3.55 (m, 1H), 1.10 (d, *J* = 6.3 Hz, 6H). ¹³C NMR {¹H} (101 MHz, DMSO-*D*₆) δ 168.21, 149.08, 143.65, 134.37, 131.03, 126.92, 126.41, 125.52, 116.36, 116.14, 113.74, 111.85, 110.87, 51.85, 43.22, 22.46.

methyl 2-(3-isopropyl-2-thioxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-1-yl)benzoate (113)



Two-necked flask was charged with **112** (2400 mg, 8.5 mmol, 1eq) THF (70 mL) was added followed by NaHCO₃. The flask was fitted with addition funnel and whole setup was flushed with argon. The addition funnel was charged with CSCl₂ (1460 mg, 12.7 mmol, 1.5 eq) in THF (20 mL). The flask was heated to 55°C and then the CSCl₂ solution was added dropwise over 10 minutes. After the addition was complete, the reaction was further stirred at 55°C for 90 minutes. Afterwards, the reaction was cooled to room temperature and water (50 mL) was added. THF layer was separated, washed with brine and evaporated to yield oily residue, which was dried overnight at high vacuum. The remaining oil (2.63 g) was crystallized from EtOH (20 mL) to yield 2 g brown crystalline solid (75%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.07 (dd, *J* = 1.6, 0.3 Hz, 1H), 7.86 (td, *J* = 7.7, 1.6 Hz, 1H), 7.75 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.71 (td, *J* = 7.7, 1.3 Hz, 1H), 7.59 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.26 (td, *J* = 8.0, 7.4, 1.2 Hz, 1H), 7.17 (td, *J* = 7.7, 1.0 Hz, 1H), 6.82 (dq, *J* = 8.0, 0.4 Hz, 1H), 5.53 (hept, *J* = 7.0 Hz, 1H), 3.47 (s, 3H), 1.58 (t, *J* = 7.1 Hz, 6H). ¹³C NMR {¹H} (101 MHz, DMSO-*D*₆) δ 169.1, 164.7, 135.1, 133.8, 133.2, 131.5, 130.1, 130.0, 129.7, 129.2, 127.8, 122.8, 110.9, 109.4, 52.3, 48.6, 19.5, 19.3.

General procedure for synthesis of amides 115a-d



Acid **7** (500 mg, 2 mmol, 1 eq) was dissolved in toluene (12 mL) and SOCl₂ (1.2 mL, 10 mmol, 5 eq) was added and the reaction was refluxed for 2 hours. After two hours, the reaction was evaporated and dissolved in CHCl₃ (10 mL). This solution was added dropwise into solution of amine (2.2 mmol, 1.1 eq) and triethylamine (310 μL, 2.2 mmol, 1.1 eq) cooled in ice bath. This reaction was stirred at room temperature for 2 hours. After 2 hours, the reaction was washed with 10% aq. HCl (3x 30 mL), 10% aq. K₂CO₃ (3x30 mL), dried with MgSO₄ and evaporated.

115a: 511 mg (90%) ¹H NMR (400 MHz, CDCl₃) δ 9.60 (s, 1H), 8.17 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.44 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.42 – 7.34 (m, 3H), 7.29 – 7.20 (m, 2H), 6.80 (ddd, *J* = 8.4, 6.9, 1.3 Hz, 1H), 1.09 (d, *J* = 28.3 Hz, 6H).

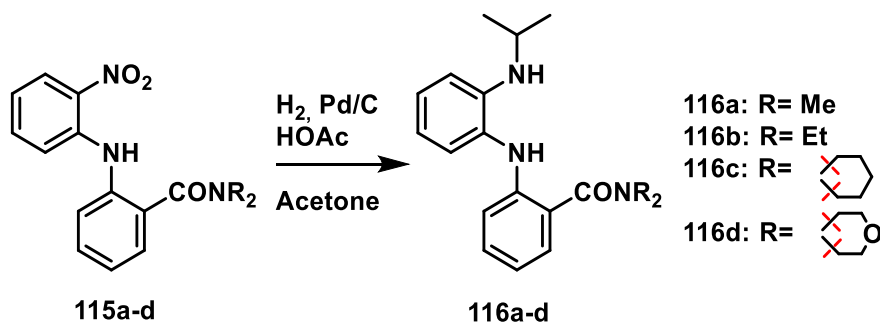
115b: 560 mg (90%) ¹H NMR (400 MHz, CDCl₃) δ 9.77 (s, 1H), 8.19 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.47 – 7.30 (m, 5H), 7.21 (td, *J* = 7.6, 1.2 Hz, 1H), 6.81 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 3.02 (d, *J* = 32.1 Hz, 6H). ¹³C NMR {¹H} (101 MHz, CDCl₃) δ 169.3, 141.8, 136.5, 135.6, 134.4, 131.0, 130.2, 128.5, 126.8, 124.9, 123.5, 118.4, 116.7, 39.0, 35.0.

115c: 680 mg (quant.) ¹H NMR (400 MHz, CDCl₃) δ 9.67 (s, 1H), 8.19 (dd, *J* = 8.6, 1.5 Hz, 1H), 7.48 – 7.33 (m, 4H), 7.29 (dd, *J* = 8.6, 1.2 Hz, 1H), 7.24 – 7.19 (m, 1H), 6.81 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H),

3.68 (s, 2H), 3.31 (s, 2H), 1.54 (d, $J = 68.7$ Hz, 6H). $^{13}\text{C NMR}\{^1\text{H}\}$ (101 MHz, CDCl_3) δ 167.8, 142.1, 136.1, 135.6, 134.3, 131.7, 130.0, 128.2, 126.8, 125.2, 123.8, 118.3, 116.6, 48.4, 42.9, 26.6, 25.7, 24.6.

115d: 664 mg (quant) $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 9.73 (s, 1H), 8.20 (dd, $J = 8.5, 1.6$ Hz, 1H), 7.48 – 7.34 (m, 4H), 7.30 – 7.20 (m, 2H), 6.84 (ddd, $J = 8.4, 7.0, 1.2$ Hz, 1H), 3.94 – 3.31 (m, 8H). $^{13}\text{C NMR}\{^1\text{H}\}$ (101 MHz, CDCl_3) δ 168.1, 141.8, 136.6, 135.7, 134.5, 130.5, 130.3, 128.5, 126.9, 125.2, 123.9, 118.6, 116.6, 66.9, 47.8, 42.4.

General procedure for synthesis of amines 116a-d by reductive amination



Three necked 250 mL flask fitted with stir bar, rubber septa and valve was charged with starting material **115a-d** (2 mmol, 1 eq), Pd/C (100 mg, 0.05 eq), acetone (80 mL) and acetic acid (200 μL , 3.5 mmol, 1.75 eq). The flask was fitted with balloon and purged with argon/vacuum three times. After the final evacuation, hydrogen gas was introduced, and the reaction as stirred rapidly at room temperature for 18 hours. After 18 hours, reaction was filtered through pad of celite, evaporated and the residue was dissolved in EtOAc (50 mL) and washed with K_2CO_3 (3x30 mL) brine and dried with MgSO_4 . The residue was purified by column chromatography.

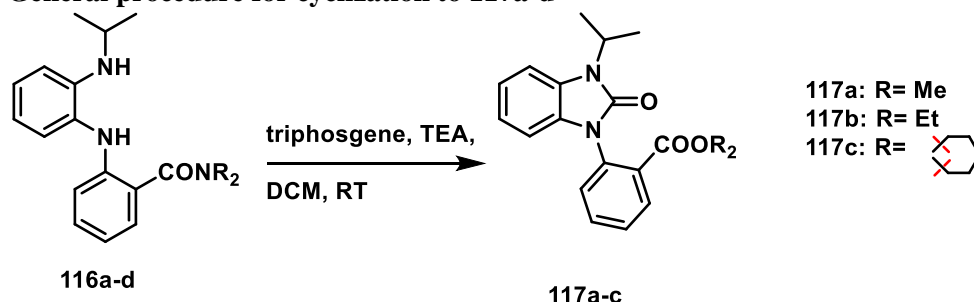
116a: Hexane: EtOAc (3:1), 260 mg (50%) $^1\text{H NMR}$ (400 MHz, $\text{DMSO-}D_6$) δ 7.16 – 7.11 (m, 2H), 7.05 – 6.98 (m, 1H), 6.96 (dd, $J = 7.7, 1.4$ Hz, 1H), 6.79 – 6.68 (m, 3H), 6.58 (td, $J = 7.5, 1.4$ Hz, 1H), 6.52 (dd, $J = 8.6, 1.0$ Hz, 1H), 4.27 (d, $J = 8.1$ Hz, 1H), 3.57 (dt, $J = 7.8, 6.3$ Hz, 1H), 2.95 (s, 6H), 1.09 (d, $J = 6.3$ Hz, 6H). $^{13}\text{C NMR}\{^1\text{H}\}$ (101 MHz, $\text{DMSO-}D_6$) δ 169.4, 143.4, 142.9, 129.8, 127.9, 127.8, 125.7, 125.3, 122.8, 117.7, 116.2, 114.8, 111.8, 43.3, 34.2, 22.6.

116b: Hexane: EtOAc (5:1), 330 mg (61%) $^1\text{H NMR}$ (400 MHz, $\text{DMSO-}D_6$) δ 7.18 – 7.08 (m, 2H), 7.02 – 6.94 (m, 2H), 6.78 (td, $J = 7.4, 1.1$ Hz, 1H), 6.69 (dd, $J = 8.1, 1.2$ Hz, 1H), 6.58 (dtd, $J = 7.5, 3.7, 1.4$ Hz, 2H), 6.51 (s, 1H), 3.60 – 3.50 (m, 1H), 3.33 (s, 4H), 1.09 (d, $J = 9.6$ Hz, 12H). $^{13}\text{C NMR}\{^1\text{H}\}$ (101 MHz, $\text{DMSO-}D_6$) δ 169.0, 142.7, 142.4, 129.5, 128.2, 127.1, 125.3, 124.4, 124.2, 118.2, 116.4, 115.2, 112.0, 43.4, 22.6, 13.7, 12.8.

116c: Hexane: EtOAc (5:1), 300mg (55%) $^1\text{H NMR}$ (400 MHz, $\text{DMSO-}D_6$) δ 7.15 – 7.09 (m, 2H), 7.01 (td, $J = 7.8, 1.5$ Hz, 1H), 6.96 (dd, $J = 7.7, 1.5$ Hz, 1H), 6.75 (td, $J = 7.4, 1.1$ Hz, 1H), 6.70 (dd, $J = 8.2, 1.2$ Hz, 1H), 6.67 (s, 1H), 6.58 (td, $J = 7.5, 1.4$ Hz, 1H), 6.50 (d, $J = 8.2$ Hz, 1H), 4.26 (d, $J = 8.1$ Hz, 1H), 3.62 – 3.52 (m, 1H), 3.44 (s, 4H), 1.54 (d, $J = 30.1$ Hz, 6H), 1.08 (d, $J = 6.3$ Hz, 6H). $^{13}\text{C NMR}\{^1\text{H}\}$ (101 MHz, $\text{DMSO-}D_6$) δ 167.9, 143.2, 142.8, 129.7, 127.9, 127.6, 125.6, 125.1, 123.1, 118.0, 116.3, 114.8, 111.8, 43.3, 25.6, 24.1, 22.6.

116d: Hexane: EtOAc (3:1), 370 mg (60%) $^1\text{H NMR}$ (400 MHz, $\text{DMSO-}D_6$) δ 7.15 (td, $J = 7.5, 1.4$ Hz, 2H), 7.05 – 6.99 (m, 1H), 6.95 (dd, $J = 7.7, 1.4$ Hz, 1H), 6.79 – 6.74 (m, 2H), 6.70 (dd, $J = 8.2, 1.1$ Hz, 1H), 6.58 (td, $J = 7.5, 1.4$ Hz, 1H), 6.53 (dd, $J = 8.8, 1.1$ Hz, 1H), 4.31 (d, $J = 8.7$ Hz, 1H), 3.63 – 3.54 (m, 5H), 3.47 (s, 3H), 1.09 (d, $J = 6.3$ Hz, 6H). $^{13}\text{C NMR}\{^1\text{H}\}$ (101 MHz, $\text{DMSO-}D_6$) δ 168.2, 143.4, 142.8, 130.0, 128.1, 127.8, 125.6, 125.2, 122.2, 118.0, 116.2, 115.1, 111.7, 66.0, 43.3, 22.6.

General procedure for cyclization to 117a-d



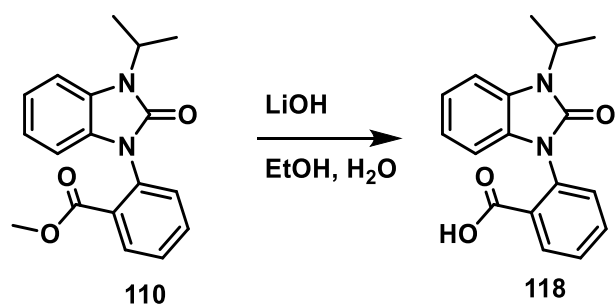
Diamine **116** (0.45 mmol, 1 eq) was dissolved in DCM (4.5 mL) and triethylamine (335 μ L, 1.35 mmol, 3 eq) was added followed by addition of triphosgene (180 mg, 0.67 mmol, 1:5 eq) and the mixture was stirred at room temperature for 1 hour. After 1 hour, the reaction was washed with 10% HCl (3x5 mL) and 10% K_2CO_3 (3x5 mL). The organic layer was evaporated and purified by column chromatography.

117a: Hexane: EtOAc 1:1.5, 120 mg (75%) 1H NMR (400 MHz, $DMSO-D_6$) δ 7.65 – 7.60 (m, 1H), 7.57 – 7.49 (m, 3H), 7.38 – 7.33 (m, 1H), 7.08 (td, $J = 7.7, 1.2$ Hz, 1H), 6.99 (td, $J = 7.7, 1.1$ Hz, 1H), 6.82 – 6.77 (m, 1H), 4.62 (hept, $J = 6.9$ Hz, 1H), 2.84 (s, 3H), 2.73 (s, 3H), 1.48 (t, $J = 6.8$ Hz, 6H). ^{13}C NMR $\{^1H\}$ (101 MHz, $DMSO-D_6$) δ 167.6, 135.2, 131.6, 130.1, 129.6, 128.7, 128.2, 128.2, 121.4, 120.7, 108.9, 108.4, 44.7, 34.3, 19.9, 19.6.

117b: Hexane: EtOAc 1:1, 120 mg (76%) 1H NMR (400 MHz, $DMSO-D_6$) δ 7.62 (td, $J = 7.5, 1.8$ Hz, 1H), 7.57 (td, $J = 7.4, 1.5$ Hz, 1H), 7.51 (ddd, $J = 7.2, 3.3, 1.6$ Hz, 2H), 7.34 (d, $J = 7.7$ Hz, 1H), 7.06 (td, $J = 7.7, 1.2$ Hz, 1H), 6.97 (td, $J = 7.7, 1.0$ Hz, 1H), 6.74 (d, $J = 7.4$ Hz, 1H), 4.63 (hept, $J = 7.0$ Hz, 1H), 3.57 – 3.21 (m, 2H), 2.93 (d, $J = 44.1$ Hz, 2H), 1.47 (t, $J = 7.0$ Hz, 6H), 0.99 (t, $J = 7.1$ Hz, 3H), 0.64 (s, 3H). ^{13}C NMR $\{^1H\}$ (101 MHz, $DMSO-D_6$) δ 166.9, 151.9, 136.3, 131.1, 131.1, 130.0, 129.8, 129.3, 128.7, 127.9, 127.5, 121.3, 120.6, 108.9, 44.5, 42.2, 37.5, 19.8, 19.8, 13.5, 11.4.

117c: Hexane :EtOAc 2:1, 134 mg (82%) 1H NMR (400 MHz, $DMSO-D_6$) δ 7.65 – 7.59 (m, 1H), 7.52 (dq, $J = 15.6, 7.1$ Hz, 3H), 7.35 (d, $J = 7.8$ Hz, 1H), 7.11 – 7.05 (m, 1H), 6.98 (t, $J = 7.6$ Hz, 1H), 6.79 (d, $J = 7.7$ Hz, 1H), 4.64 (hept, $J = 6.8$ Hz, 1H), 3.33 (s, 3H), 3.21 (s, 3H), 1.48 (dd, $J = 10.1, 6.9$ Hz, 6H), 1.42 (s, 4H).

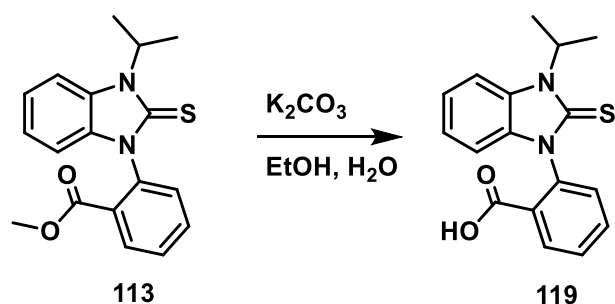
2-(3-isopropyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)benzoic acid (**118**)



Starting material (2.14 g, 6.9 mmol, 1 eq) was dissolved in EtOH (35 mL) and water (20 mL). $LiOH \cdot H_2O$ (1.65 g, 69 mmol, 10 eq) was added and the suspension was heated to 55°C for 3.5 hrs. Afterwards, the mixture was cooled to room temperature, diluted with 50 mL of water, and extracted with DCM (2x 25 mL). The aq. Layer was then acidified with HCl (5 mL) and extracted with EtOAc (3x 50 mL). Organic extracts were combined and dried with $MgSO_4$ and evaporated. The residue was dissolved in EtOH, evaporated and after drying under high vacuum 1.75 g of light foam was isolated (85%). 1H NMR (400 MHz, $DMSO-D_6$) δ 8.00 (dd, $J = 7.8, 1.3$ Hz, 1H), 7.77 (td, $J = 7.6, 1.6$ Hz, 1H), 7.63 – 7.56 (m, 2H), 7.39 – 7.36 (m, 1H), 7.08 (td, $J = 7.7, 1.2$ Hz, 1H), 6.99 (td, $J = 7.7, 1.1$ Hz, 1H), 6.77 (dd, $J = 7.8, 0.8$

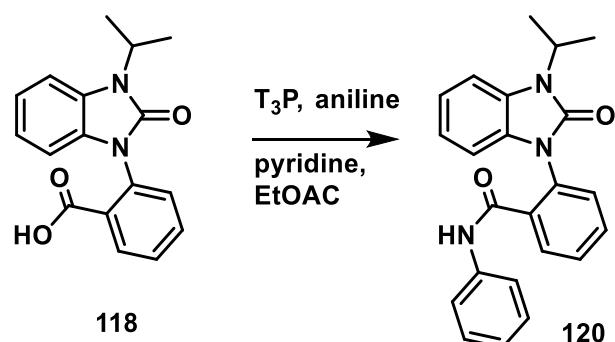
Hz, 1H), 4.65 (hept, $J = 6.9$ Hz, 1H), 1.49 (t, $J = 6.8$ Hz, 6H). $^{13}\text{C NMR}\{^1\text{H}\}$ (101 MHz, $\text{DMSO-}D_6$) δ 166.5, 152.4, 133.6, 133.0, 131.3, 129.9, 129.1, 128.6, 121.3, 120.8, 109.1, 107.8, 44.5, 19.9, 19.8.

2-(3-isopropyl-2-thioxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)benzoic acid (119)



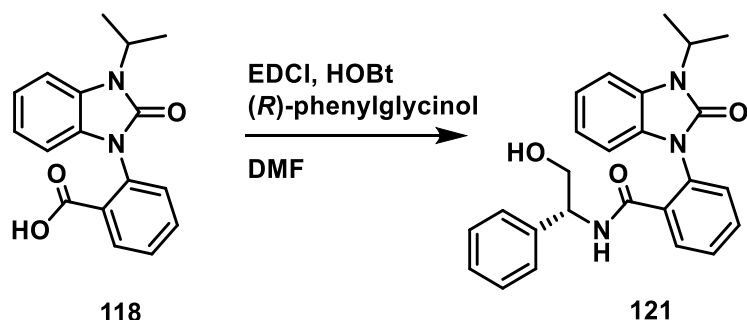
113 (1.53 g, 4.69 mmol, 1 eq) was dissolved in EtOH (30 mL) and water (37 mL) was added, followed by K_2CO_3 (6.5 g, 46.9 mmol, 10 eq). The mixture was refluxed for 18 hours. After 18 hours, the reaction was cooled to room temperature, ethanol was evaporated under reduced pressure and the remaining solution was acidified by HCl while cooling and stirring. The mixture was left stirring for 30 minutes and the precipitated solid was isolated by filtration yielding 1.3 g of white solid (92%). $^1\text{H NMR}$ (400 MHz, $\text{DMSO-}D_6$) δ 8.07 (dd, $J = 7.8, 1.5$ Hz, 1H), 7.81 (td, $J = 7.6, 1.6$ Hz, 1H), 7.72 (d, $J = 8.0$ Hz, 1H), 7.68 (td, $J = 7.7, 1.3$ Hz, 1H), 7.53 (dd, $J = 7.8, 1.1$ Hz, 1H), 7.23 (td, $J = 7.8, 1.2$ Hz, 1H), 7.15 (td, $J = 7.8, 1.0$ Hz, 1H), 6.80 – 6.76 (m, 1H), 5.54 (hept, $J = 7.1$ Hz, 1H), 1.57 (dd, $J = 12.3, 7.1$ Hz, 5H). $^{13}\text{C NMR}\{^1\text{H}\}$ (101 MHz, $\text{DMSO-}D_6$) δ 169.3, 165.7, 135.3, 133.5, 133.4, 131.5, 130.5, 130.2, 130.1, 129.6, 122.7, 122.6, 110.9, 109.5, 48.5, 19.6, 19.4.

2-(3-isopropyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)-N-phenylbenzamide (120)



118 (50 mg, 0.17 mmol, 1 eq) was dissolved in EtOAc (600 μL), pyridine (282 μL was added) followed by T3P (50 wt.% in EtOAc, 110 μL , 1 mmol, 1 eq) and aniline (17.5 μL , 0.19 mmol, 1.1 eq). The mixture was stirred at room temperature for 4 hours. After 4 hours, the reaction was diluted with EtOAc (10 mL), extracted with 10% HCl (3x 10 mL), 10% K_2CO_3 (3x 10 mL) and brine (1x 10 mL). Organic layers were combined, dried with MgSO_4 and evaporated to yield 40 mg of oil (63%) $^1\text{H NMR}$ (500 MHz, $\text{DMSO-}D_6$) δ 10.34 (s, 1H), 7.82 – 7.78 (m, 2H), 7.72 (td, $J = 7.7, 1.5$ Hz, 1H), 7.65 – 7.58 (m, 3H), 7.54 (d, $J = 7.7$ Hz, 2H), 7.34 (d, $J = 7.8$ Hz, 1H), 7.25 (t, $J = 7.9$ Hz, 2H), 7.07 (td, $J = 7.7, 1.2$ Hz, 1H), 7.05 – 7.01 (m, 2H), 6.99 (td, $J = 7.7, 1.0$ Hz, 1H), 6.89 – 6.85 (m, 2H), 4.59 (hept, $J = 6.9$ Hz, 1H), 1.43 (dd, $J = 14.6, 6.9$ Hz, 6H). $^{13}\text{C NMR}\{^1\text{H}\}$ (101 MHz, CDCl_3) δ 165.0, 154.8, 154.3, 144.6, 138.4, 138.2, 131.7, 131.1, 130.5, 130.2, 129.5, 129.0, 128.5, 124.3, 122.3, 121.9, 119.6, 109.7, 45.8, 20.4.

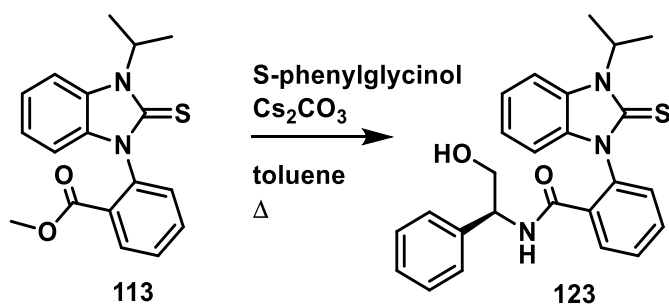
(R)-N-(2-hydroxy-1-phenylethyl)-2-(3-isopropyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)benzamide (121)



118 (150 mg, 0.5 mmol, 1eq) was dissolved in DMF (2.5 mL). EDCI (198 mg, 1 mmol, 2 eq) was added followed by HOBt (153 mg, 1 mmol, 2eq) and R-(-)-phenylglycinol (76 mg, 0.55 mmol, 1.1 eq). The reaction was stirred at room temperature for 18 hours. After 18 hours, the solution was diluted with EtOAc (15 mL), washed with 10% HCl (3x 15 mL), 10% K₂CO₃ (3x 15 mL) and brine (1x 15 mL). The EtOAc solution was dried with MgSO₄ and evaporated to yield 160 mg of light foam (77%). No chromatographic separation of the diastereomers was possible. ¹H NMR (400 MHz, CDCl₃) δ 7.93 – 7.86 (m, 0.3H), 7.67 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.57 (qd, *J* = 8.1, 1.6 Hz, 2H), 7.51 – 7.42 (m, 2H), 7.41 – 7.27 (m, 5H), 7.22 – 7.09 (m, 3H), 7.09 – 7.04 (m, 1H), 7.01 (dd, *J* = 7.8, 1.4 Hz, 1H), 6.99 – 6.95 (m, 1H), 6.93 (d, *J* = 8.5 Hz, 1H), 6.78 (dd, *J* = 7.8, 1.1 Hz, 0.3H), 5.14 (ddd, *J* = 8.4, 5.9, 3.7 Hz, 1H), 4.94 (td, *J* = 6.7, 4.0 Hz, 0.3H), 4.77 (h, *J* = 7.0 Hz, 1H), 3.93 – 3.85 (m, 1H), 4.61 (p, *J* = 7.0 Hz, 0.3H), 3.81 (dd, *J* = 11.4, 4.1 Hz, 0.3zH), 3.73 (dd, *J* = 11.8, 6.0 Hz, 1H), 1.61 (d, *J* = 7.0 Hz, 6H), 1.47 (d, *J* = 7.0 Hz, 1H), 1.34 (d, *J* = 7.0 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 167.6, 167.2, 153.7, 153.6, 139.2, 136.1, 131.7, 131.2, 130.8, 130.6, 130.2, 129.5, 129.2, 129.1, 129.0, 128.9, 128.6, 128.4, 128.4, 127.9, 127.6, 127.1, 126.8, 122.2, 121.8, 109.8, 109.7, 109.5, 109.4, 66.4, 65.5, 57.6, 56.0, 45.8, 45.6, 20.5, 20.4, 20.3, 20.2.

(S)-N-(2-hydroxy-1-phenylethyl)-2-(3-isopropyl-2-thioxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)benzamide (123)

Method 1)

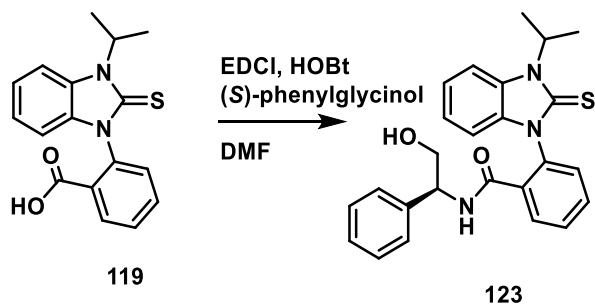


113 (650 mg, 2 mmol, 1 eq) was dissolved in toluene (5 mL), Cs₂CO₃ (650 mg, 2 mmol, 1 eq) was added followed by S-(+)-phenylglycinol (550 mg, 2 mmol, 2 eq). Reaction mixture was heated to 100°C for 18 hours. After 18 hours, the mixture was cooled to room temperature, toluene (20 mL) and water (20 mL) were added, and layers were separated. Organic layer was washed with water (1x20 mL) and brine (2x 20 mL), dried with MgSO₄ and evaporated. The residue was purified by column chromatography (Hexane: EtOAc gradient 2:1 → 3:2 → 1:1). Two diastereomers were isolated as white foam: product eluting first: 210 mg (48%), product eluting second: 140 mg (32%).

Product eluting first: ¹H NMR (400 MHz, CDCl₃) δ 7.78 – 7.69 (m, 1H), 7.71 – 7.56 (m, 3H), 7.52 (dt, *J* = 8.2, 0.8 Hz, 1H), 7.37 – 7.21 (m, 7H), 7.18 (td, *J* = 7.8, 1.0 Hz, 1H), 6.85 (dt, *J* = 7.9, 0.8 Hz, 1H), 5.72 (hept, *J* = 7.0 Hz, 1H), 5.00 (ddd, *J* = 8.5, 6.2, 4.6 Hz, 1H), 3.62 – 3.49 (m, 2H), 1.68 (dd, *J* =

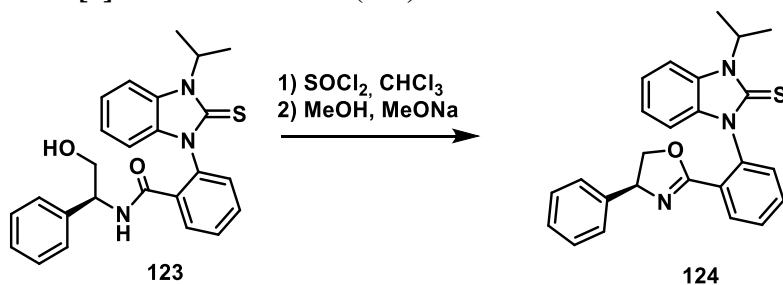
7.1, 2.5 Hz, 6H). $^{13}\text{C NMR}\{^1\text{H}\}$ (101 MHz, CDCl_3) δ 168.9, 166.7, 138.5, 137.2, 134.2, 132.7, 131.8, 130.5, 130.4, 129.7, 129.7, 128.8, 127.8, 127.0, 123.8, 123.6, 111.2, 110.9, 66.2, 56.3, 50.0, 20.3, 20.0. **Product eluting second:** $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.02 – 7.90 (m, 2H), 7.72 – 7.60 (m, 2H), 7.53 (dt, $J = 8.2, 0.9$ Hz, 1H), 7.35 – 7.23 (m, 2H), 7.16 (ddd, $J = 8.4, 7.5, 1.0$ Hz, 1H), 7.08 – 7.02 (m, 1H), 6.95 – 6.90 (m, 2H), 6.75 (ddd, $J = 8.0, 1.0, 0.6$ Hz, 1H), 6.68 – 6.64 (m, 2H), 5.59 (hept, $J = 7.0$ Hz, 1H), 4.88 (td, $J = 6.1, 4.0$ Hz, 1H), 3.83 (dd, $J = 11.7, 3.9$ Hz, 1H), 3.75 (dd, $J = 11.7, 6.3$ Hz, 1H), 1.64 (d, $J = 7.1$ Hz, 3H), 1.41 (d, $J = 7.1$ Hz, 3H). $^{13}\text{C NMR}\{^1\text{H}\}$ (101 MHz, CDCl_3) δ 169.2, 166.5, 138.4, 136.3, 134.2, 132.5, 132.3, 131.2, 130.7, 130.5, 129.9, 128.3, 127.3, 126.4, 123.9, 123.6, 111.1, 110.9, 66.3, 57.0, 49.9, 20.3, 19.8.

Method 2)



119 (100 mg, 0.3 mmol, 1eq) was dissolved in DMF (3 mL). EDCI (14 mg, 0.6 mmol, 2 eq) was added followed by HOBt.H₂O (92 mg, 0.6 mmol, 2 eq) and S-(+)-phenylglycinol (40 mg, 0.33 mmol, 1.1 eq). Reaction was stirred at room temperature for 18 hours. After 18 hours, reaction was diluted with EtOAc (15 mL), washed with 10% HCl (3x 15 mL), 10% K₂CO₃ (3x 15 mL) and brined. Organic layer was dried with MgSO₄ and purified by column chromatography. (Hexane: EtOAc gradient 2:1 → 3:2 → 1:1). Two diastereomers were isolated as white foam: product eluting first: 32 mg (44%), product eluting second: 30 mg (41%).

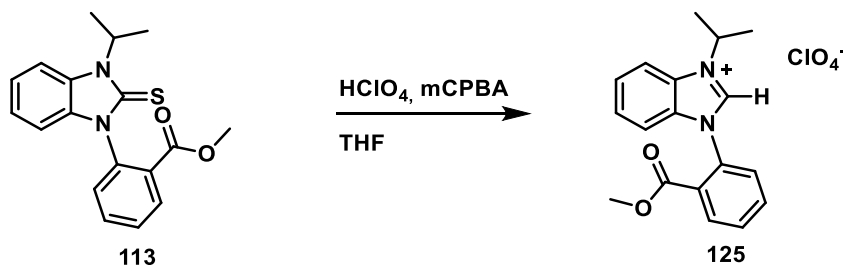
(S)-1-isopropyl-3-(2-(4-phenyl-4,5-dihydrooxazol-2-yl)phenyl)-1,3-dihydro-2H-benzo[d]imidazole-2-thione (**124**)



123 (215 mg, 0.5 mmol, 1eq) was dissolved in CHCl_3 (5 mL) and SOCl_2 (181 μL , 2.5 mmol, 5 eq) was added. The reaction was stirred at room temperature for 60 minutes. Afterwards, the mixture was evaporated, dissolved in CHCl_3 and evaporated again. The residue was dissolved in MeOH (5 mL) and sodium methoxide was added (135 mg, 2.5 mmol, 5 eq). The reaction was stirred at room temperature for 7 hours. After 7 hours, the reaction was diluted with water and extracted with DCM. No chromatographic separation was possible to separate the diastereomers.

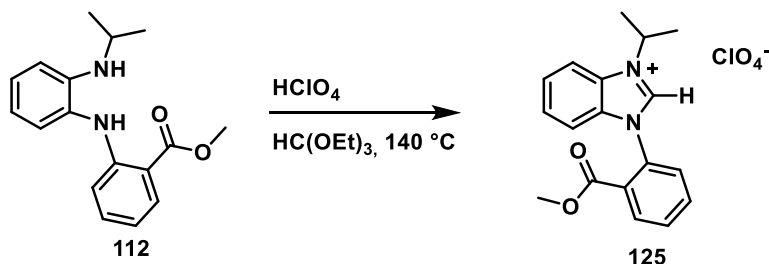
3-isopropyl-1-(2-(methoxycarbonyl)phenyl)-1*H*-benzo[*d*]imidazol-3-ium perchlorate (125)

Method 1)



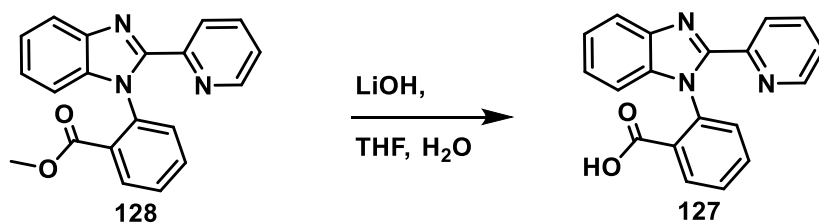
113 (163 mg, 0.5 mmol, 1 eq) was dissolved in THF (2 mL). The solution was cooled in acetone-dry ice bath (-78 °C). To the cooled solution, mCPBA (75%, 401 mg, 1.75 mmol, 3.5 eq) was added portion wise. To the resulting suspension, 70% aq. HClO₄ (214 μL, 2.5 mmol 5 eq) was added dropwise. The reaction was stirred in the bath for 3.5 hours and then it was warmed to room temperature and left stirring for 16 hours. The resulting suspension was filtered, washed with diethyl ether and water, and dried to yield 73 mg of white solid (42%). ¹H NMR (400 MHz, DMSO-*D*₆) δ 10.23 (s, 1H), 8.32 – 8.29 (m, 1H), 8.27 (d, *J* = 8.4 Hz, 1H), 8.04 (ddd, *J* = 7.9, 7.3, 1.6 Hz, 1H), 7.76 (ddd, *J* = 8.4, 7.3, 1.0 Hz, 1H), 7.67 (ddd, *J* = 8.3, 7.3, 1.0 Hz, 1H), 7.51 (dt, *J* = 8.3, 0.8 Hz, 1H), 5.23 (hept, *J* = 6.6 Hz, 1H), 3.60 (s, 3H), 1.69 (s (br, 6H)). ¹³C NMR{¹H} (101 MHz, DMSO-*D*₆) δ 163.9, 142.1, 134.7, 132.6, 132.2, 132.1, 131.8, 130.0, 129.6, 127.6, 126.8, 126.7, 114.2, 113.1, 52.8, 50.9, 22.0, 21.5.

Method 2)



112 (142 mg, 0.5 mmol, 1eq) was suspended in HC(OEt)₃ followed by addition of HClO₄ (90 μL, 2 eq). The reaction was heated in DrySyn heating block set up to 140°C. After 2 hours, the reaction was cooled to room temperature and evaporated. To the residue MeOH (2 mL) was added and the mixture was cooled in dry ice. The solid was filtered, washed with ether and dried. Yielding 121 mg (70%)

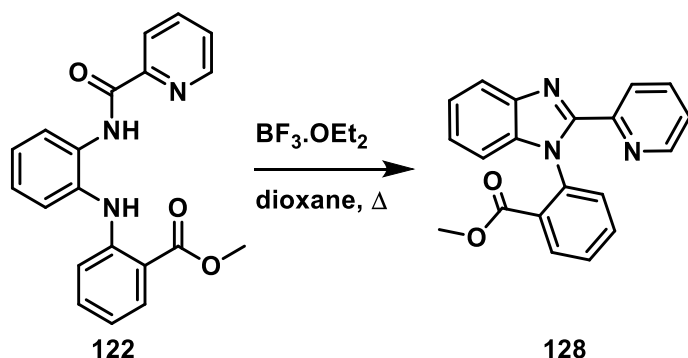
2-(2-(pyridin-2-yl)-1*H*-benzo[*d*]imidazol-1-yl)benzoic acid (127)



128 (1.65 g, 5 mmol, 1 eq) was dissolved in THF (45 mL) and water (36 mL). LiOH·H₂O (420 mg, 10 mmol, 2 eq) was added and the reaction was stirred at room temperature for 22 hours. Afterwards, the reaction was acidified with conc. HCl (863 μL, 10 mmol, 2 eq) and THF was evaporated under reduced pressure. The solid material was filtered and dried. Yield 1.42 g of brown solid, (90%). ¹H NMR (400 MHz, DMSO-*D*₆) δ 12.55 (s, 1H), 8.25 (dt, *J* = 8.0, 1.1 Hz, 1H), 8.21 (ddd, *J* = 4.8, 1.9, 1.0 Hz, 1H), 8.02 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.91 (td, *J* = 7.7, 1.8 Hz, 1H), 7.84 – 7.75 (m, 1H), 7.76 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.64 (td, *J* = 7.6, 1.3 Hz, 1H), 7.53 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.34 – 7.31 (m, 1H), 7.31 – 7.28 (m, 1H), 7.27 – 7.23 (m, 1H), 7.02 – 6.93 (m, 1H). ¹³C NMR{¹H} (101 MHz, DMSO-*D*₆) δ 206.4, 165.9, 150.3, 149.2, 148.3, 142.3, 137.9, 137.4, 136.9, 133.0, 131.1, 129.5, 129.4, 128.7, 124.0, 123.8,

123.6, 122.5, 119.5, 110.5, 30.6. **HRMS** ESI[M+H]⁺ calculated for C₁₉H₁₄O₂N₃: 316.1081, found: 316.1078

methyl 2-(2-(pyridin-2-yl)-1*H*-benzo[*d*]imidazol-1-yl)benzoate (128)



122 (10.7 g, 30.8 mmol, 1 eq) was dissolved in dioxane (150 mL) and $\text{BF}_3 \cdot \text{OEt}_2$ (9.75 mL, 77.1 mmol, 2.5 eq) was added. The reaction was refluxed for 16 hours. After 16 hours the reaction was cooled to room temperature and 10% aq. Na_2CO_3 (50 mL) was added. The white precipitate was filtered away and the filtrate was concentrated under reduced pressure. The remaining solution was extracted with DCM (3x 20 mL). Combined organic extracts were dried with MgSO_4 and evaporated to yield 10 g of gray solid (quantitative). ¹H NMR (400 MHz, DMSO-*D*₆) δ 8.25 (d, $J = 7.9$ Hz, 1H), 8.22 – 8.18 (m, 1H), 7.99 (dd, $J = 7.8, 1.5$ Hz, 1H), 7.92 (td, $J = 7.7, 1.6$ Hz, 1H), 7.85 – 7.78 (m, 2H), 7.66 (td, $J = 7.6, 1.1$ Hz, 1H), 7.61 (d, $J = 7.8$ Hz, 1H), 7.36 – 7.23 (m, 3H), 7.00 (d, $J = 7.7$ Hz, 1H), 3.32 (s, 3H). ¹³C NMR{¹H} (101 MHz, DMSO-*D*₆) δ 165.3, 150.8, 149.5, 148.9, 142.8, 138.2, 137.8, 137.6, 134.0, 131.4, 130.1, 129.3, 128.8, 124.7, 124.4, 124.4, 123.2, 120.1, 111.0, 52.4. **HRMS** ESI[M+H]⁺ calculated for C₂₀H₁₆O₂N₃: 330.1237, found: 330.1234

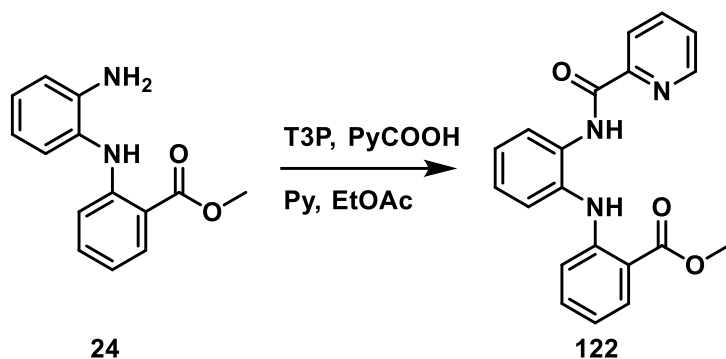
RESOLUTION OF 128

3900 mg of **128** (racemate) was suspended in acetonitrile (190 mL) and L-dibenzoyl-tartaric acid (4140 mg, 1 eq) was added. This mixture was refluxed until fully dissolved (15 min). After full dissolution, the mixture was allowed to cool to room temperature while stirring. After 2.5 hours, the precipitate was filtered away. The filtrate was evaporated. The precipitate (A) contains product with approx. 15:85 er., filtrate (B) contains the product in approx. 95:5 er.

The precipitated material (A) was again recrystallized from acetonitrile (140 mL) by addition of the solid salt into boiling (prolonged heating causes racemization) acetonitrile. After full dissolution, the mixture was left to cool to room temperature with stirring. After 2 hours, the solid material was filtered away to yield solid in approx. 2:98 er.

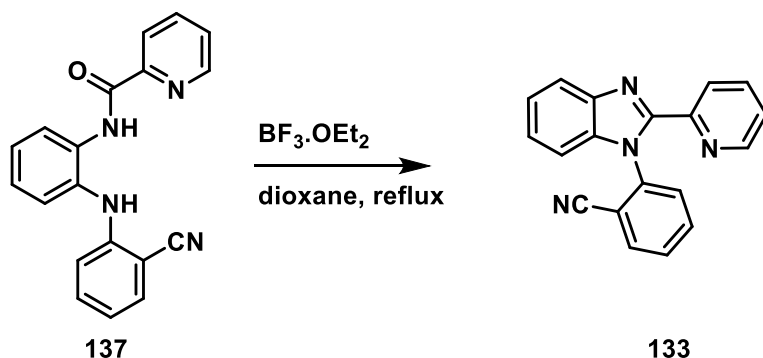
The evaporated filtrate (B) was dissolved in EtOAc and extracted twice with 10. aq. NaOH and once with brine and dried with MgSO_4 . After removal of MgSO_4 by filtration, the solution was carefully concentrated under reduced pressure (to approx. 10-20% of original volume) which induced precipitation of solid material which was collected by filtration to yield 890 mg (45%) of enantiopure ligand **128**. The absolute configuration was determined by X-Ray crystallography to be (P).

methyl 2-((2-(picolinamido)phenyl)amino)benzoate (122)



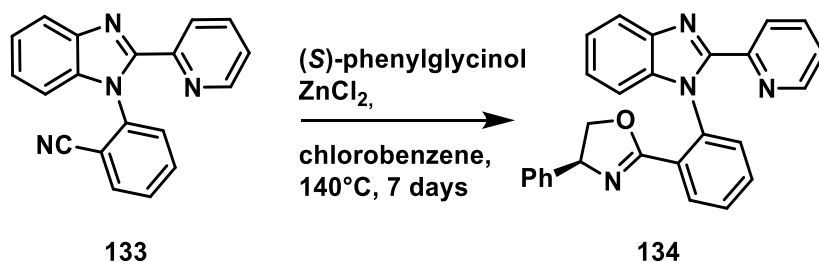
24 (14 g, 57.8 mmol, 1 eq) was dissolved in EtOAc (385 mL) and pyridine (192 mL) was added (Total volume 578 mL, $c = 0.1\text{M}$). T3P (50% wt solution in EtOAc, 36.7g, 1 eq) was added followed by 2-picolinic acid. The reaction was stirred at room temperature for 16 hrs. After 16 hours, the reaction was washed with 10% HCl (3x 500 mL) and 10% K_2CO_3 (3x 500 mL), water (1x 500 mL) and brine. Organic layer was dried with MgSO_4 and evaporated to yield 16.1 g of gray solid (80%). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 10.50 (s, 1H), 9.19 (s, 1H), 8.59 (dd, $J = 8.5, 1.4$ Hz, 1H), 8.41 (ddd, $J = 4.7, 1.7, 0.9$ Hz, 2H), 8.24 (dt, $J = 7.8, 1.0$ Hz, 1H), 8.00 (dd, $J = 8.0, 1.6$ Hz, 1H), 7.89 – 7.79 (m, 1H), 7.37 (ddd, $J = 7.6, 4.8, 1.2$ Hz, 1H), 7.35 – 7.30 (m, 2H), 7.23 (ddd, $J = 8.7, 7.1, 1.7$ Hz, 1H), 7.21 – 7.12 (m, 1H), 6.76 – 6.65 (m, 4H), 3.94 (s, $J = 2.8$ Hz, 3H). $^{13}\text{C NMR}\{^1\text{H}\}$ (101 MHz, CDCl_3) δ 169.1, 162.3, 150.0, 149.5, 148.2, 137.5, 134.7, 134.5, 131.5, 130.8, 127.2, 127.0, 126.3, 124.8, 122.3, 121.2, 117.4, 114.6, 112.2, 52.0. HRMS ESI[M+H] $^+$ calculated for $\text{C}_{20}\text{H}_{18}\text{O}_3\text{N}_3$: 348.1343, found: 348.1344

2-(2-(pyridin-2-yl)-1H-benzo[d]imidazol-1-yl)benzonitrile (133)



137 (245 mg, 0.5 mmol, 1 eq) was dissolved in dioxane (5 mL) and $\text{BF}_3 \cdot \text{OEt}_2$ (183 μL , 1.3 mmol, 2.5 eq) was added. The reaction was refluxed for 16 hours. After 16 hours, the reaction was cooled to room temperature, quenched with 10% aq. K_2CO_3 (5 mL) and further diluted with water (5 mL). The resulting solution was extracted with DCM (3x 10 mL). Combined organic extracts were dried with MgSO_4 , evaporated and purified by column chromatography (hexane: EtOAc 4:1) to yield 180 mg of product as gray solid (80%). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.44 (dt, $J = 8.0, 1.0$ Hz, 1H), 8.20 (ddd, $J = 4.8, 1.7, 0.9$ Hz, 1H), 7.93 (dt, $J = 8.1, 1.0$ Hz, 1H), 7.84 – 7.75 (m, 3H), 7.60 (td, $J = 7.7, 1.2$ Hz, 1H), 7.55 (s, 1H), 7.38 (ddd, $J = 8.1, 7.2, 1.2$ Hz, 1H), 7.35 – 7.30 (m, 1H), 7.22 (ddd, $J = 7.6, 4.8, 1.2$ Hz, 1H), 7.08 (dt, $J = 8.0, 0.9$ Hz, 1H). $^{13}\text{C NMR}\{^1\text{H}\}$ (101 MHz, CDCl_3) δ 150.3, 149.1, 148.5, 143.0, 141.3, 137.6, 137.0, 133.8, 133.6, 129.0, 128.8, 124.6, 124.4, 124.1, 123.8, 120.6, 115.8, 113.1, 110.4.

(S)-4-phenyl-2-(2-(2-(pyridin-2-yl)-1H-benzo[d]imidazol-1-yl)phenyl)-4,5-dihydrooxazole (134)

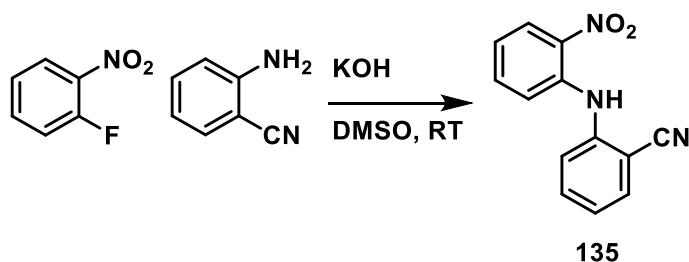


ZnCl₂ (40 mg, 0.06 mmol, 0.125 eq) was melted under vacuum with heat gun and let cool to room temperature. **133** (150 mg, 0.5 mmol, 1 eq) was dissolved in chlorobenzene (5 mL) and melted ZnCl₂ was added, followed by (*S*)-phenylglycinol. This mixture was refluxed for 7 days. After 7 days, the reaction was cooled to room temperature, partially evaporated and MeOH (5 mL) was added. This solution was then diluted with water (25 mL) and extracted with EtOAc (3x 20 mL). Combined extracts were washed with brine, dried with MgSO₄ and evaporated. The mixture was purified by preparative HPLC.

Product eluting first: ¹H NMR (400 MHz, CDCl₃) δ 8.31 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H), 8.16 (dt, *J* = 8.0, 1.0 Hz, 1H), 8.10 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.91 – 7.88 (m, 2H), 7.68 (dtd, *J* = 13.5, 7.7, 1.7 Hz, 3H), 7.55 (ddd, *J* = 14.9, 7.6, 1.3 Hz, 2H), 7.34 (ddd, *J* = 8.1, 7.2, 1.2 Hz, 1H), 7.31 – 7.26 (m, 1H), 7.20 – 7.15 (m, 6H), 7.12 – 7.09 (m, 2H), 6.84 – 6.80 (m, 3H), 4.90 (dd, *J* = 10.1, 8.7 Hz, 1H), 4.29 (dd, *J* = 10.2, 8.5 Hz, 1H), 3.57 (t, *J* = 8.6 Hz, 1H). ¹³C NMR{¹H} (101 MHz, CDCl₃) δ 163.3, 151.2, 149.6, 148.9, 142.8, 141.7, 138.2, 137.3, 136.4, 131.9, 131.3, 129.7, 128.6, 128.6, 127.5, 126.7, 126.6, 124.1, 124.0, 123.7, 123.1, 120.2, 110.9, 74.8, 69.7.

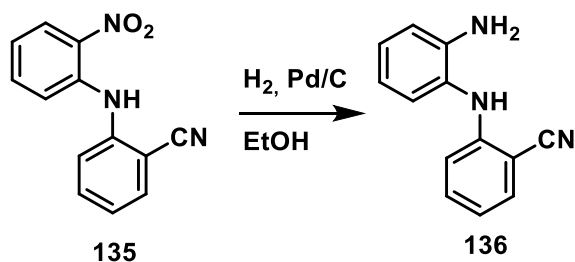
Product eluting second: ¹H NMR (400 MHz, CDCl₃) δ 8.31 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H), 8.22 (dt, *J* = 8.0, 1.0 Hz, 1H), 8.17 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.90 – 7.87 (m, 1H), 7.70 (ddd, *J* = 6.8, 6.2, 1.6 Hz, 1H), 7.68 – 7.64 (m, 1H), 7.56 (td, *J* = 7.7, 1.4 Hz, 1H), 7.51 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.35 (ddd, *J* = 8.1, 7.2, 1.2 Hz, 1H), 7.27 (ddd, *J* = 8.2, 7.2, 1.2 Hz, 1H), 7.19 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 7.18 – 7.03 (m, 4H), 6.65 – 6.61 (m, 2H), 5.02 – 4.95 (m, 1H), 4.28 – 4.19 (m, 1H), 3.68 (t, *J* = 8.6 Hz, 1H). ¹³C NMR{¹H} (101 MHz, CDCl₃) δ 163.0, 151.1, 149.7, 148.9, 142.8, 141.9, 138.3, 137.4, 136.5, 132.0, 131.4, 129.6, 128.6, 128.5, 127.3, 126.4, 126.4, 124.1, 123.9, 123.7, 123.0, 120.1, 110.8, 74.7, 69.4.

2-((2-nitrophenyl)amino)benzonitrile (135)



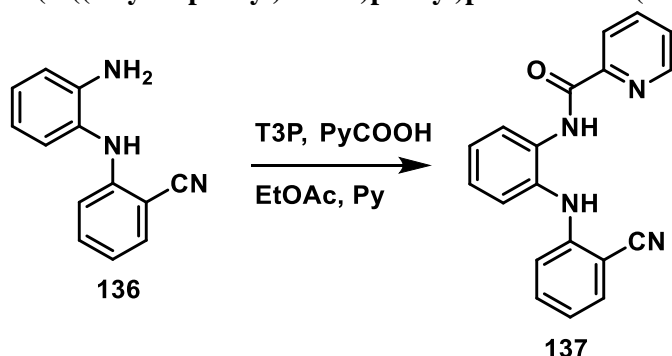
2-fluoronitrobenzene (3.75 mL, 35.6 mmol, 1 eq) was dissolved in DMSO (37 mL) and 2-aminobenzonitrile (4200 mg, 35.6 mmol, 1 eq) was added. To this solution solid KOH (4200 mg, 74.75 mmol, 2.1 eq) was added. The reaction was stirred at room temperature for 24 hours. After 24 hours, the reaction mixture was poured into cold water (150 mL). The precipitate was filtered and dried in oven overnight. Yield 6.3 g (75%). ¹H NMR (400 MHz, CDCl₃) δ 9.70 – 9.48 (m, 1H), 8.25 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.71 (ddd, *J* = 7.8, 1.6, 0.5 Hz, 1H), 7.63 – 7.57 (m, 1H), 7.51 – 7.45 (m, 2H), 7.30 – 7.22 (m, 3H), 6.97 (ddd, *J* = 8.4, 7.1, 1.3 Hz, 1H). ¹³C NMR{¹H} (101 MHz, CDCl₃) δ 142.7, 140.3, 135.7, 135.5, 134.1, 134.0, 127.0, 124.9, 122.8, 120.1, 117.1, 116.5, 107.4.

2-((2-aminophenyl)amino)benzonitrile (136)



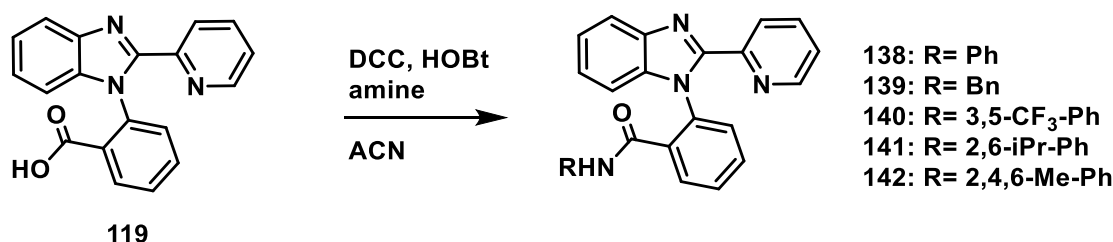
3-necked round-bottomed flask equipped with stir bar, valve and rubber septa was charged with 10% palladium on charcoal (665 mg, 0.05 eq). **135** (3 g, 12.5 mmol, 1 eq) was added, followed by EtOH (200 mL). The system was evacuated and purged with nitrogen 4 times. After the last purge, the flask was evacuated and filled with hydrogen gas. The suspension was stirred 4 hours. After the reaction was complete, celite was added and the suspension was filtered. The filtrate was evaporated to yield 2.45 g of solid (93%) $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.47 (dd, $J = 7.8, 1.6$ Hz, 1H), 7.34 – 7.29 (m, 1H), 7.12 (ddd, $J = 14.9, 7.7, 1.4$ Hz, 2H), 6.83 (dd, $J = 8.0, 1.3$ Hz, 1H), 6.78 (tdd, $J = 7.7, 2.0, 1.3$ Hz, 2H), 6.56 (d, $J = 8.5$ Hz, 1H), 5.95 (s, 1H), 3.83 (s, 2H). $^{13}\text{C NMR}\{^1\text{H}\}$ (101 MHz, CDCl_3) δ 148.9, 143.5, 134.3, 132.8, 128.2, 127.8, 124.8, 119.2, 118.4, 117.9, 116.4, 113.5, 96.9.

N-2-((2-cyanophenyl)amino)phenylpicolinamide (137)



136 (2450 mg, 11.7 mmol, 1 eq) was dissolved in EtOAc (80 mL). Pyridine (40 mL) was added followed by T3P (50% wt. in EtOAc, 7.45 mL, 11.7 mmol, 1 eq) and 2-picolinic acid (1570 mg, 12.9 mmol, 1.1 eq). The reaction was stirred for 16 hours at room temperature. After 16 hours, more T3P (50% wt. in EtOAc, 7.45 mL, 11.7 mmol, 1 eq) was added to fully convert the starting material to the product. After 2 hours, the reaction was filtered to yield 1.15 g of the product. The filtrate was washed with 10% HCl (1 x 100 mL). The organic extract was cooled in dry ice and the solid material was filtered to yield another 980 mg of solid material. The remaining solution was evaporated and recrystallized from EtOAc (42 mL). In total, 2.81 g of solid material was isolated (75%). $^1\text{H NMR}$ (400 MHz, $\text{DMSO-}D_6$) δ 10.59 (s, 1H), 8.59 (ddd, $J = 4.8, 1.7, 0.9$ Hz, 1H), 8.19 (d, $J = 6.8$ Hz, 2H), 8.14 (dt, $J = 7.8, 1.1$ Hz, 1H), 8.05 (td, $J = 7.7, 1.7$ Hz, 1H), 7.64 (ddd, $J = 7.6, 4.8, 1.3$ Hz, 1H), 7.61 (dd, $J = 7.8, 1.4$ Hz, 1H), 7.39 – 7.27 (m, 3H), 7.22 (ddd, $J = 8.6, 6.9, 1.5$ Hz, 1H), 6.83 (td, $J = 7.7, 1.0$ Hz, 1H), 6.63 (d, $J = 8.4$ Hz, 1H). $^{13}\text{C NMR}\{^1\text{H}\}$ (101 MHz, $\text{DMSO-}D_6$) δ 161.9, 149.2, 148.7, 148.4, 138.3, 134.3, 133.7, 133.1, 132.2, 127.2, 126.2, 125.9, 125.3, 122.4, 122.2, 119.2, 117.6, 115.2, 98.0.

General procedure for the amidation synthesis of 138-142.



Acid **119** (100 mg, 0.22 mmol, 1 eq) was dissolved in acetonitrile (6 mL) HOBt.H₂O (38 mg, 0.25 mmol, 1.1 eq) was added followed by DCC (52 mg, 0.25 mmol, 1.1 eq) and amine (0.25 mmol, 1.1 eq). The reaction was stirred at room temperature for 16 hours. Afterwards, the precipitate was removed by filtration and the filtrate was evaporated. The residue was dissolved in EtOAc (20 mL) and washed with 10% K₂CO₃ (3x 20 mL). Organic layer was washed with brine, dried with MgSO₄ and evaporated. The product was purified by suitable methods.

N-phenyl-2-(2-(pyridin-2-yl)-1H-benzo[d]imidazol-1-yl)benzamide (138): The evaporated residue was dissolved in MeOH (1 mL) and water (1 mL) was added. After sonication, solid product precipitated and was filtered. Yield: 66 mg (76%). ¹H NMR (400 MHz, DMSO-*D*₆) δ 10.40 (s, 1H), 8.45 (dd, *J* = 4.7, 1.5 Hz, 1H), 8.15 (d, *J* = 7.8 Hz, 1H), 7.91 (td, *J* = 7.8, 1.8 Hz, 1H), 7.82 (dd, *J* = 7.2, 2.1 Hz, 1H), 7.79 – 7.75 (m, 1H), 7.65 (pd, *J* = 7.6, 1.6 Hz, 2H), 7.46 – 7.38 (m, 2H), 7.33 – 7.25 (m, 2H), 7.22 (d, *J* = 8.2 Hz, 2H), 7.15 (t, *J* = 7.8 Hz, 2H), 7.06 – 7.01 (m, 1H), 6.96 (t, *J* = 7.1 Hz, 1H). ¹³C NMR{¹H} (101 MHz, DMSO-*D*₆) δ 164.6, 150.4, 148.7, 142.2, 138.5, 137.9, 137.6, 135.3, 134.8, 131.4, 129.0, 128.9, 128.9, 128.6, 123.9, 123.7, 122.8, 119.7, 119.5, 110.8. HRMS ESI[M+H]⁺ calculated for C₂₅H₁₉O₁N₄: 391.1553, found: 391.1553

N-benzyl-2-(2-(pyridin-2-yl)-1H-benzo[d]imidazol-1-yl)benzamide (139): The evaporated residue was dissolved in MeOH (1 mL) and water (1 mL) was added. After sonication, solid product precipitated and was filtered. Yield: 70 mg (79%). ¹H NMR (400 MHz, DMSO-*D*₆) δ 8.81 (t, *J* = 6.0 Hz, 1H), 8.28 (dd, *J* = 5.0, 1.8 Hz, 1H), 8.18 (d, *J* = 7.6 Hz, 1H), 7.93 (td, *J* = 7.7, 1.9 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.75 – 7.71 (m, 1H), 7.64 – 7.56 (m, 2H), 7.38 – 7.31 (m, 3H), 7.26 (td, *J* = 7.8, 1.0 Hz, 1H), 7.10 – 6.99 (m, 3H), 6.97 (d, *J* = 8.0 Hz, 1H), 6.70 (d, *J* = 7.1 Hz, 2H), 5.57 (d, *J* = 8.0 Hz, 1H), 4.16 – 4.02 (m, 2H). ¹³C NMR{¹H} (101 MHz, DMSO-*D*₆) δ 166.0, 150.6, 148.9, 148.6, 142.3, 138.7, 138.1, 137.4, 135.0, 131.0, 129.1, 128.9, 128.7, 128.0, 126.4, 124.4, 123.8, 122.7, 119.6, 110.9, 42.1. HRMS ESI[M+H]⁺ calculated for C₂₆H₂₁O₁N₄: 405.1710, found: 405.1710

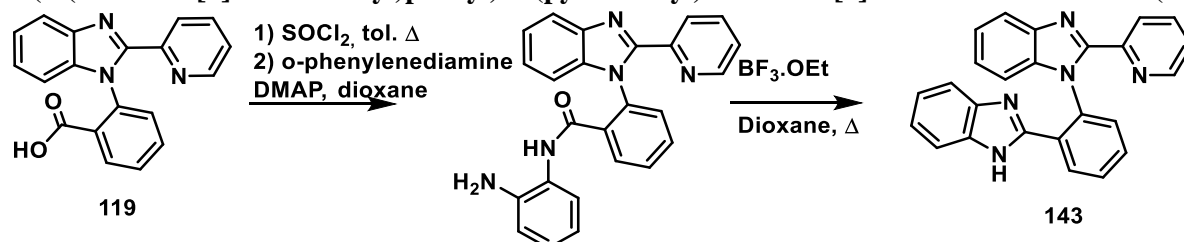
N-(3,5-bis(trifluoromethyl)phenyl)-2-(2-(pyridin-2-yl)-1H-benzo[d]imidazol-1-yl)benzamide (140): Residue was purified by column chromatography (Hexane: EtOAc 1:1). The fractions containing product were combined, evaporated, and dissolved in small amount of DCM and the residual dicyclohexylurea was removed by filtration. Isolated 60 mg (52%) of oil ¹H NMR (400 MHz, DMSO-*D*₆) δ 10.70 (s, 1H), 8.37 (ddd, *J* = 4.8, 1.5, 0.8 Hz, 1H), 8.06 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.95 (s, 2H), 7.87 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.81 – 7.77 (m, 1H), 7.77 – 7.75 (m, 1H), 7.74 (dd, *J* = 4.5, 2.8 Hz, 1H), 7.73 – 7.68 (m, 2H), 7.61 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.35 – 7.26 (m, 3H), 7.12 (dd, *J* = 6.8, 1.8 Hz, 1H). ¹³C NMR{¹H} (101 MHz, DMSO-*D*₆) δ 165.4, 150.2, 148.8, 148.7, 142.2, 140.4, 137.7, 137.0, 135.5, 133.6, 131.9, 130.47 (q, *J* = 32.9 Hz), 129.0, 128.7, 128.6, 123.08 (q, *J* = 272.8 Hz), 124.12, 124.1, 123.9, 122.8, 119.4 (d, *J* = 4.2 Hz), 116.5, 110.8. ¹⁹F NMR (376 MHz, CDCl₃) δ -63.1.

N-(2,6-diisopropylphenyl)-2-(2-(pyridin-2-yl)-1H-benzo[d]imidazol-1-yl)benzamide (141): Residue was purified by column chromatography (Hexane: EtOAc 1.1:1). Yield: 155 mg (65%). ¹H NMR (400 MHz, CDCl₃) δ 10.00 (s, 1H), 8.32 (d, *J* = 7.9 Hz, 1H), 8.32 – 8.26 (m, 1H), 7.98 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.89 (td, *J* = 7.8, 1.7 Hz, 1H), 7.60 (td, *J* = 7.5, 0.9 Hz, 1H), 7.40 (td, *J* = 7.6, 1.4 Hz, 2H), 7.33 (td, *J* = 7.8, 7.3, 1.0 Hz, 1H), 7.28 (ddd, *J* = 7.5, 5.0, 1.0 Hz, 1H), 7.21 – 7.11 (m, 2H), 7.08 (d, *J* = 7.4 Hz, 1H), 6.93 (d, *J* = 7.4 Hz, 1H), 6.90 – 6.83 (m, 1H), 3.18 (p, *J* = 6.9 Hz, 1H), 1.62 (dq, *J* = 16.5, 9.4, 8.1 Hz, 1H), 1.29 (d, *J* = 6.7 Hz, 3H), 1.20 (d, *J* = 6.8 Hz, 3H),

0.51 (d, $J = 6.6$ Hz, 3H), 0.36 (d, $J = 6.7$ Hz, 3H). $^{13}\text{C NMR}\{^1\text{H}\}$ (101 MHz, CDCl_3) δ 167.0, 148.7, 147.2, 145.2, 138.7, 138.1, 137.2, 134.0, 131.2, 131.2, 131.0, 130.2, 129.9, 128.5, 128.2, 125.5, 125.3, 125.2, 125.2, 124.6, 124.1, 123.7, 123.0, 120.2, 111.9, 29.8, 29.2, 28.2, 23.8, 23.6, 23.0.

***N*-mesityl-2-(2-(pyridin-2-yl)-1*H*-benzo[*d*]imidazol-1-yl)benzamide (142)**: Residue was purified by column chromatography (Hexane: EtOAc 1.5:1 \rightarrow 1:1). Yield 69 (25%). $^1\text{H NMR}$ (400 MHz, $\text{DMSO-}D_6$) δ 9.75 (s, 1H), 8.36 – 8.33 (m, 1H), 8.24 (d, $J = 7.9$ Hz, 1H), 7.97 (td, $J = 7.8, 1.7$ Hz, 1H), 7.87 (dd, $J = 7.6, 1.5$ Hz, 1H), 7.80 (d, $J = 7.4$ Hz, 1H), 7.68 (td, $J = 7.6, 1.2$ Hz, 1H), 7.62 (td, $J = 7.7, 1.6$ Hz, 1H), 7.41 – 7.35 (m, 2H), 7.31 (td, $J = 8.1, 7.7, 1.4$ Hz, 1H), 7.26 (td, $J = 7.7, 7.3, 1.3$ Hz, 1H), 6.97 (d, $J = 7.4$ Hz, 1H), 6.70 (s, 2H), 2.11 (s, 3H), 1.59 (br.s, 6H). $^{13}\text{C NMR}\{^1\text{H}\}$ (101 MHz, $\text{DMSO-}D_6$) δ 164.5, 150.4, 148.9, 148.6, 137.6, 135.6, 134.9, 134.7, 131.6, 131.2, 129.4, 129.3, 128.8, 128.2, 124.5, 124.4, 123.9, 122.8, 119.6, 111.0, 20.4, 17.3.

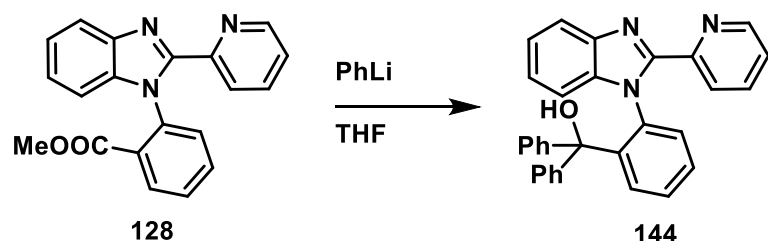
1-(2-(1*H*-benzo[*d*]imidazol-2-yl)phenyl)-2-(pyridin-2-yl)-1*H*-benzo[*d*]imidazole (143)



119 (160 mg, 0.5 mmol, 1eq) was dissolved in toluene, SOCl_2 (61 μL , 1 mmol, 2 eq) was added and the mixture was refluxed for 30 minutes. After 30 minutes, the reaction was cooled to room temperature, evaporated and the residue was suspended in dioxane (5 mL). This suspension was slowly added into the solution of *o*-phenylenediamine (60 mg, 0.55 mmol, 1.1 eq) and DMAP (70 mg, 0.55 mmol, 1.1eq) in dioxane (3 mL). The reaction was stirred at room temperature for 20 hours. After 20 hours, reaction was filtered and $\text{BF}_3\cdot\text{OEt}_2$ (250 μL , 2 mmol, 4 eq) was added to the filtrate. This mixture was then refluxed for 16 hours. After 16 hours, the reaction was cooled to room temperature, water (10 mL) was added followed by 10% aq. NaOH (10 mL). This mixture was extracted with EtOAc (3x 20 mL). Organic extracts were combined, washed with brine, dried with MgSO_4 and evaporated. The residue was then dissolved in EtOAc (1.5 mL) and precipitated with hexanes (7 ml). Yield: 50 mg (25%).

$^1\text{H NMR}$ (400 MHz, $\text{DMSO-}D_6$) δ 12.21 (s, 1H), 8.23 (ddd, $J = 4.8, 1.8, 0.9$ Hz, 1H), 8.02 – 7.93 (m, 1H), 7.77 (ddt, $J = 9.1, 7.9, 1.0$ Hz, 2H), 7.73 – 7.64 (m, 2H), 7.63 (td, $J = 7.7, 1.8$ Hz, 1H), 7.62 – 7.53 (m, 1H), 7.32 – 7.19 (m, 4H), 7.20 (ddd, $J = 8.3, 7.1, 1.2$ Hz, 1H), 7.12 – 7.00 (m, 2H), 7.01 (ddd, $J = 8.3, 7.1, 1.3$ Hz, 1H), 6.49 (dd, $J = 5.7, 3.5$ Hz, 1H), 6.36 (dd, $J = 5.7, 3.4$ Hz, 1H).

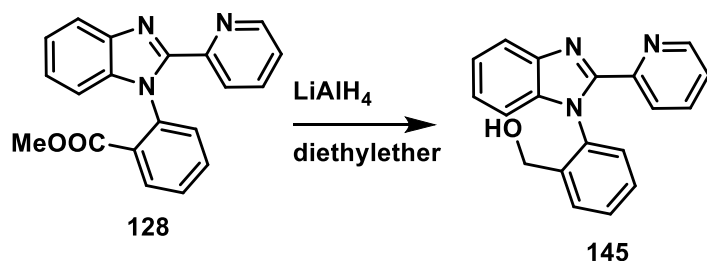
diphenyl(2-(2-(pyridin-2-yl)-1*H*-benzo[*d*]imidazol-1-yl)phenyl)methanol (144)



128 (110 mg, 0.33 mmol, 1 eq) was dissolved in dry THF (3 mL) and cooled in ice/salt/water bath to 0 $^\circ\text{C}$ and PhLi (1.9M in Bu_2O , 0.52 mL, 1 mmol, 3 eq) was added dropwise. The reaction was stirred in the ice bath for 30 minutes. Afterwards, 20% aq. NH_4Cl (2.5 mL) was added, followed by diethyl ether (5 mL). Organic layer was separated, and aq. layer was further extracted with diethyl ether (3x 10 mL). Combined organic layers were dried with MgSO_4 and evaporated. The residue was purified by column chromatography (Hexane: EtOAc 1:1) to yield 75 mg of gray solid (50%) $^1\text{H NMR}$ (400 MHz, $\text{DMSO-}D_6$) δ 8.21 (dd, $J = 6.9, 1.8$ Hz, 1H), 7.97 – 7.84 (m, 2H), 7.62 (d, $J = 8.0$ Hz, 1H), 7.58 (td, $J = 6.8, 5.9, 4.0$ Hz, 2H), 7.43 – 7.23 (m, 6H), 7.10 (t, $J = 7.6$ Hz, 1H), 7.09 – 6.94 (m, 4H), 6.95 – 6.83 (m, 4H), 6.76 – 6.68 (m, 4H), 6.41 (d, $J = 8.1$ Hz, 1H), 5.73 (s, 1H). $^{13}\text{C NMR}\{^1\text{H}\}$ (101 MHz, $\text{DMSO-}D_6$) δ

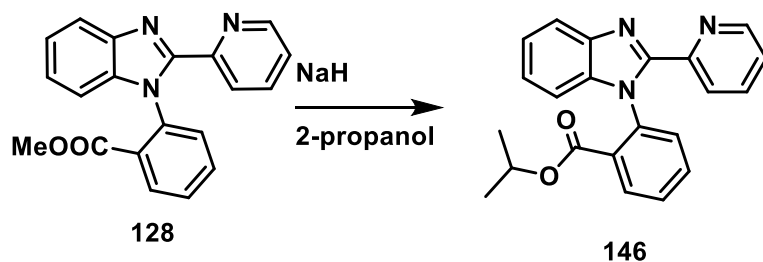
154.5, 150.2, 149.9, 146.4, 146.3, 143.7, 138.9, 137.9, 137.7, 137.4, 131.8, 131.3, 128.9, 128.4, 128.3, 127.7, 127.4, 127.3, 127.0, 126.7, 126.6, 126.4, 126.3, 122.4, 121.4, 119.6, 118.6, 111.3, 81.5. **HRMS** ESI[M+H]⁺ calculated for C₃₁H₂₄O₁N₃: 454.1914, found: 454.1914

(2-(2-(pyridin-2-yl)-1H-benzo[d]imidazol-1-yl)phenyl)methanol (145)



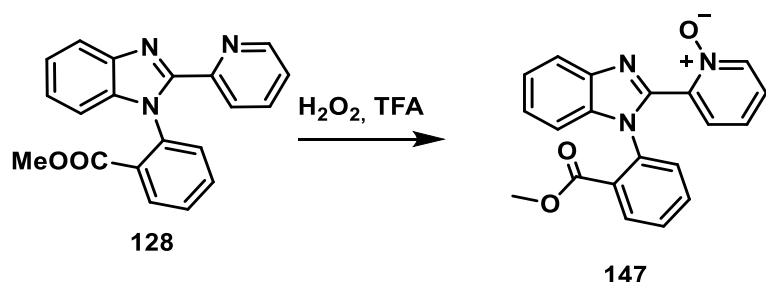
128 (55 mg, 0.16 mmol, 1 eq) was added slowly into the suspension of LiAlH₄ (25 mg, 0.65 mmol, 4 eq) in diethyl ether (4 mL). The reaction was stirred at room temperature for 2 hours. After 2 hours, water (25 μ L) was added, followed by 10% aq. NaOH (75 μ L) and water (75 μ L). The solid precipitate was filtered through celite. Celite was washed with diethyl ether and the filtrate was evaporated. The residue was purified by column chromatography (hexane: EtOAc 2:1) to yield 23 mg clear oil (48%). ¹H NMR (400 MHz, CDCl₃) δ 8.27 (ddd, *J* = 4.9, 1.5, 0.9 Hz, 1H), 8.24 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.92 (d, *J* = 8.1 Hz, 1H), 7.85 (td, *J* = 7.8, 1.7 Hz, 1H), 7.71 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.51 (td, *J* = 7.6, 1.3 Hz, 1H), 7.37 (ddd, *J* = 8.1, 7.3, 1.2 Hz, 1H), 7.35 – 7.21 (m, 3H), 6.97 – 6.88 (m, 1H), 6.90 (dd, *J* = 7.8, 1.2 Hz, 1H), 5.41 (d, *J* = 9.1 Hz, 1H), 4.64 (d, *J* = 11.3 Hz, 1H), 4.39 (dd, *J* = 11.8, 6.4 Hz, 1H).

isopropyl 2-(2-(pyridin-2-yl)-1H-benzo[d]imidazol-1-yl)benzoate (146)



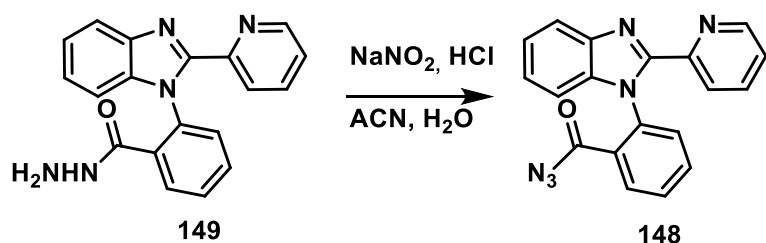
128 (50 mg, 0.15 mmol, 1 eq) was dissolved in 2-propanol and catalytic amount of NaH was added. The reaction was stirred at room temperature for 4 hours. After 4 hours, the reaction was quenched with conc. HCl (1 drop) and evaporated. The residue was dissolved in EtOAc (5 mL) and washed with 10% aq. K₂CO₃ (3x 5 mL), brined, dried with MgSO₄, and evaporated to yield 41 mg of clear foam (77%). ¹H NMR (400 MHz, CDCl₃) δ 8.31 (d, *J* = 7.9 Hz, 1H), 8.24 (d, *J* = 4.3 Hz, 1H), 8.13 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.73 (td, *J* = 7.8, 1.8 Hz, 1H), 7.67 (td, *J* = 7.6, 1.7 Hz, 1H), 7.58 (td, *J* = 7.6, 1.3 Hz, 1H), 7.45 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.35 – 7.30 (m, 1H), 7.27 – 7.22 (m, 1H), 7.16 (ddd, *J* = 7.4, 4.8, 0.9 Hz, 1H), 7.00 (d, *J* = 8.0 Hz, 1H), 4.72 (hept, *J* = 6.2 Hz, 1H), 0.76 (d, *J* = 6.2 Hz, 3H), 0.53 (d, *J* = 6.2 Hz, 3H). ¹³C NMR{¹H} (101 MHz, CDCl₃) δ 165.0, 150.6, 149.5, 148.6, 142.7, 138.6, 137.8, 136.4, 132.8, 131.7, 130.3, 129.9, 128.7, 124.0, 123.9, 123.6, 122.9, 120.0, 110.7, 21.1, 20.8.

2-(1-(2-(methoxycarbonyl)phenyl)-1H-benzo[d]imidazol-2-yl)pyridine 1-oxide (147)



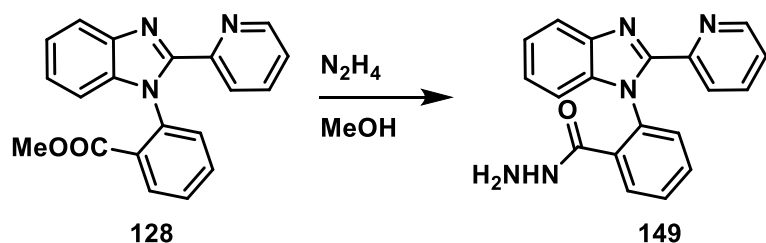
128 (110 mg, 0.33 mmol, 1 eq) was dissolved in TFA (830 μL) and 30% H_2O_2 (530 μL) was added. Reaction was stirred at room temperature for 22 hours. After 22 hours, the reaction was diluted with EtOAc (20 mL) and washed with 10% K_2CO_3 (3x 10 mL), saturated $\text{Na}_2\text{S}_2\text{O}_3$ (3x 10 mL), brine and dried with MgSO_4 and evaporated to yield 110 mg of solid (95%). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.03 – 8.00 (m, 1H), 7.96 – 7.92 (m, 1H), 7.92 – 7.88 (m, 1H), 7.79 – 7.76 (m, 1H), 7.70 – 7.65 (m, 2H), 7.51 (td, $J = 7.6, 1.3$ Hz, 1H), 7.36 – 7.27 (m, 2H), 7.29 – 7.19 (m, 2H), 7.12 (ddd, $J = 7.7, 1.5, 0.7$ Hz, 1H), 3.47 (s, 3H).

2-(2-(pyridin-2-yl)-1H-benzo[d]imidazol-1-yl)benzoyl azide (148)



149 (76 mg, 0.23 mmol, 1 eq) was dissolved in acetonitrile (6 mL) and water (2 mL) and cooled in ice bath. Conc. HCl (348 μL , 1 mmol, 4 eq) was added. To this solution, solution of NaNO_2 (32 mg, 0.46 mmol, 2 eq) in water (2 mL) was added dropwise. The reaction slowly changed color from yellow to brown orange. The mixture was stirred in the ice bath for 60 minutes. After 60 minutes, 10% aq. K_2CO_3 (10 mL) was added, and the mixture separated into two layers. Organic layer was separated and the aqueous layer was extracted with EtOAc (3x 10 mL). Combined organics were dried with MgSO_4 and evaporated to yield 56 mg of oil (72%). $^1\text{H NMR}$ (400 MHz, $\text{DMSO-}D_6$) δ 8.31 – 8.27 (m, 1H), 8.22 – 8.18 (m, 1H), 8.06 (dd, $J = 7.9, 1.4$ Hz, 1H), 7.93 (td, $J = 7.8, 1.8$ Hz, 1H), 7.88 (td, $J = 7.6, 1.6$ Hz, 1H), 7.83 (d, $J = 7.8$ Hz, 1H), 7.70 (td, $J = 7.7, 1.1$ Hz, 1H), 7.62 (dd, $J = 7.8, 0.9$ Hz, 1H), 7.37 – 7.30 (m, 2H), 7.27 (t, $J = 7.4$ Hz, 1H), 6.99 (d, $J = 7.8$ Hz, 1H). $^{13}\text{C NMR}\{^1\text{H}\}$ (101 MHz, $\text{DMSO-}D_6$) δ 170.4, 149.9, 148.9, 148.4, 142.3, 137.6, 137.2, 134.9, 131.0, 130.0, 129.1, 128.2, 124.2, 123.9, 123.8, 122.8, 119.6, 110.5.

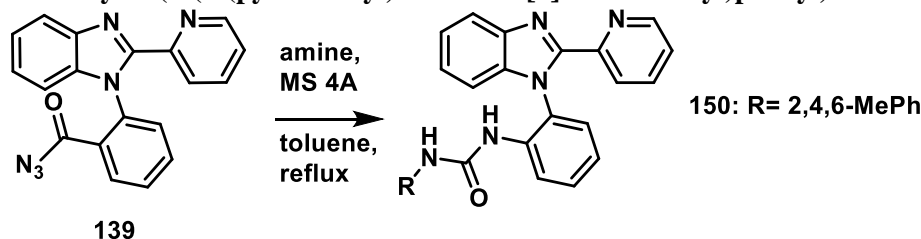
2-(2-(pyridin-2-yl)-1H-benzo[d]imidazol-1-yl)benzohydrazide (149)



128 (1.95 g, 5.9 mmol, 1 eq) was dissolved in MeOH (53 mL) and hydrazine hydrate (35 mL) was added. The solution was stirred at room temperature for 16 hours. After 16 hours, MeOH was evaporated, and the resulting suspension was filtered and dried to yield 1.5 g (77%) of yellow solid. $^1\text{H NMR}$ (400 MHz, $\text{DMSO-}D_6$) δ 9.37 (s, 1H), 8.31 (ddd, $J = 4.8, 1.7, 0.9$ Hz, 1H), 8.18 (dt, $J = 7.9, 1.0$ Hz, 1H), 7.94 (td, $J = 7.8, 1.8$ Hz, 1H), 7.79 (d, $J = 7.4$ Hz, 1H), 7.64 – 7.60 (m, 1H), 7.60 – 7.55 (m,

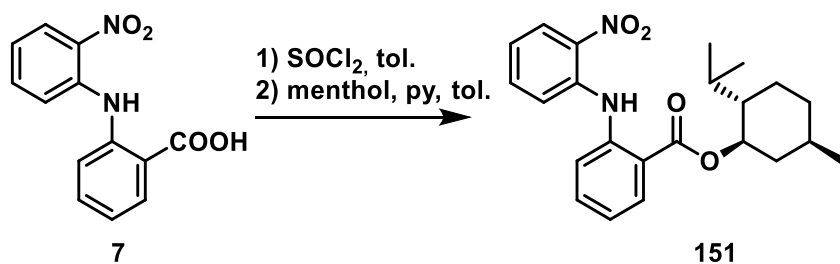
2H), 7.40 – 7.34 (m, 2H), 7.30 (td, $J = 7.6, 1.3$ Hz, 1H), 7.25 (td, $J = 7.6, 7.2, 1.3$ Hz, 1H), 6.97 (dd, $J = 7.6, 1.2$ Hz, 1H), 4.05 (s, 2H). $^{13}\text{C NMR}\{^1\text{H}\}$ (101 MHz, $\text{DMSO-}D_6$) δ 165.4, 150.8, 149.1, 148.7, 142.3, 137.9, 137.3, 135.2, 133.5, 131.1, 129.1, 128.8, 128.7, 124.4, 124.2, 123.7, 122.7, 119.6, 110.9.

1-mesityl-3-(2-(2-(pyridin-2-yl)-1H-benzo[d]imidazol-1-yl)phenyl)urea (150)



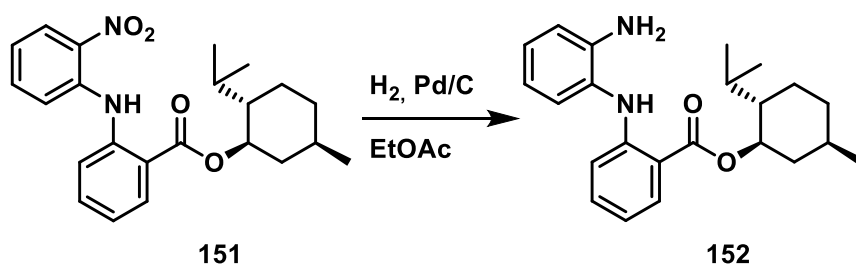
Freshly prepared azide **139** (155 mg, 0.5 mmol, 1 eq) was dissolved in dry toluene (20 mL, dried over activated sieves). Powdered molecular sieves (140 mg) were added followed by 2,4,6-trimethylaniline (1 mmol, 2 eq). The reaction was refluxed for 16 hours. After 16 hours, molecular sieves were removed by filtration through celite. The filtrate was evaporated and purified by column chromatography. Purified by gradient DCM \rightarrow DCM: MeOH 20:1 to yield 177 mg of solid (82%) $^1\text{H NMR}$ (400 MHz, $\text{DMSO-}D_6$) δ 8.30 (d, $J = 21.9$ Hz, 2H), 8.12 (d, $J = 7.8$ Hz, 1H), 7.99 – 7.91 (m, 1H), 7.86 (d, $J = 7.9$ Hz, 2H), 7.77 (s, 1H), 7.45 – 7.31 (m, 3H), 7.28 (t, $J = 7.5$ Hz, 1H), 7.01 (m, 3H), 6.78 (s, 2H), 2.16 (s, 3H), 1.91 (s, 6H).

(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl 2-((2-nitrophenyl)amino)benzoate (151)



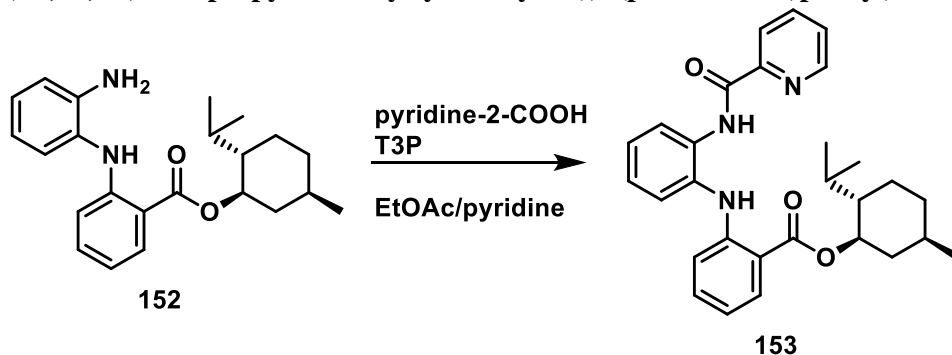
Acid **7** (256 mg, 1 mmol, 1 eq) was suspended in toluene (10 mL) and SOCl_2 (600 μL , 8.3 mmol, 8.3 eq) was added. The mixture was refluxed for 2 hours. After two hours, the reaction was cooled to room temperature and evaporated. The intermediate acyl chloride was dissolved in toluene (10 mL) and was added dropwise to solution of (1R,2S,5R)-menthol (125 mg, 0.8 mmol, 0.8 eq), pyridine (160 μL , 2 mmol, 2 eq) in toluene (5 mL). After the addition was complete, the mixture was refluxed for 24 hours. After 24 hours, the reaction mixture was cooled to room temperature, washed with 10% aq. K_2CO_3 (3x 10 mL), brine, dried with MgSO_4 and evaporated. The residue was purified by column chromatography (toluene) to yield 150 mg of dark oil (40%) $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 11.12 (s, 1H), 8.17 (dd, $J = 8.4, 1.6$ Hz, 1H), 8.05 (dd, $J = 8.0, 1.6$ Hz, 1H), 7.60 (dd, $J = 8.6, 1.2$ Hz, 1H), 7.51 (dd, $J = 8.3, 1.1$ Hz, 1H), 7.43 (ddt, $J = 8.7, 7.2, 1.9$ Hz, 2H), 7.05 (ddd, $J = 8.2, 7.2, 1.2$ Hz, 1H), 6.93 (ddd, $J = 8.4, 7.1, 1.3$ Hz, 1H), 5.01 (td, $J = 10.9, 4.4$ Hz, 1H), 2.15 (ddt, $J = 9.5, 4.4, 2.7$ Hz, 1H), 1.96 (pd, $J = 7.0, 2.7$ Hz, 1H), 1.79 – 1.68 (m, 2H), 1.67 – 1.47 (m, 2H), 1.11 (dt, $J = 12.5, 5.3$ Hz, 2H), 0.99 – 0.94 (m, 1H), 1.01 – 0.86 (m, 6H), 0.79 (d, $J = 6.9$ Hz, 3H). $^{13}\text{C NMR}\{^1\text{H}\}$ (101 MHz, CDCl_3) δ 166.7, 142.5, 137.5, 134.8, 133.3, 132.1, 126.8, 121.9, 119.9, 119.4, 119.2, 119.0, 75.5, 47.2, 41.0, 34.4, 31.6, 26.6, 23.6, 22.1, 20.9, 16.6.

(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl 2-((2-aminophenyl)amino)benzoate (152)



3-necked round-bottomed flask equipped with stir bar, valve and rubber septa was charged with 10% palladium on charcoal (46 mg, 0.05 eq). **153** (350 mg, 0.88 mmol, 1 eq) was added, followed by EtOAc (10 mL). The system was evacuated and purged with nitrogen 4 times. After the last purge, the flask was evacuated and filled with hydrogen gas. The suspension was stirred for 4 hours. After the reaction was complete, celite was added and the suspension was filtered. The filtrate was evaporated to yield 220 mg (70 %) of oily product. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 9.08 (s, 1H), 7.97 (dd, $J = 8.1, 1.6$ Hz, 1H), 7.27 (ddd, $J = 8.6, 7.1, 1.7$ Hz, 1H), 7.16 (dd, $J = 7.8, 1.4$ Hz, 1H), 7.09 (ddd, $J = 7.9, 7.4, 1.5$ Hz, 1H), 6.86 (dd, $J = 8.0, 1.3$ Hz, 1H), 6.79 (td, $J = 7.6, 1.4$ Hz, 1H), 6.69 (ddd, $J = 8.1, 7.1, 1.1$ Hz, 1H), 6.65 (dd, $J = 8.5, 0.8$ Hz, 1H), 4.93 (td, $J = 10.9, 4.4$ Hz, 1H), 3.91 (s, 2H), 2.19 – 2.13 (m, 1H), 2.04 – 1.99 (m, 1H), 1.78 – 1.70 (m, 2H), 1.58 (ddd, $J = 15.1, 7.7, 3.2$ Hz, 2H), 1.20 – 1.07 (m, 2H), 0.97 – 0.92 (m, 7H), 0.82 (d, $J = 7.0$ Hz, 3H). $^{13}\text{C NMR}\{^1\text{H}\}$ (101 MHz, CDCl_3) δ 168.3, 149.6, 142.8, 134.3, 131.5, 127.6, 127.0, 126.5, 119.3, 116.5, 116.3, 113.9, 111.8, 74.5, 47.3, 41.2, 34.4, 31.6, 26.6, 23.7, 22.2, 20.9, 16.6.

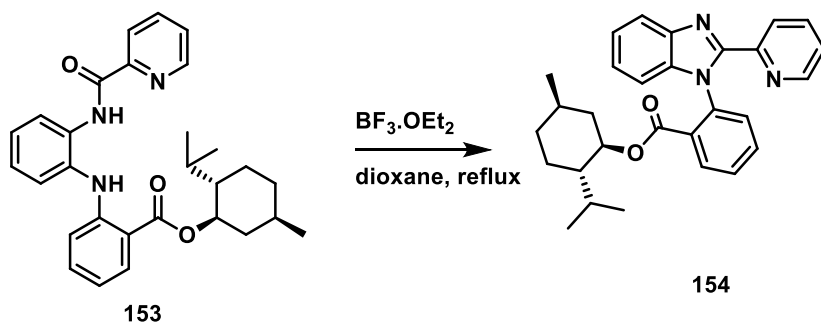
(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl 2-((2-(picolinamido)phenyl)amino)benzoate (153)



Ester **154** (120 mg, 0.32 mmol, 1eq) was dissolved in EtOAc (2 mL), pyridine (1 mL) was added followed by T3P (50% wt. in EtOAc, 203 μL , 1eq) and 2-picolinic acid (44 mg, 0.36 mmol, 1.1 eq). Reaction was stirred at room temperature for 16 hours. After 16 hours, it was diluted with EtOAc (10 mL) and extracted with 10% HCl (3x 10 mL), brine, dried with MgSO_4 and evaporated to yield 131 mg (87%). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 10.53 (s, 1H), 9.32 (s, 1H), 8.60 (dd, $J = 8.2, 1.4$ Hz, 1H), 8.39 (ddd, $J = 4.7, 1.7, 0.9$ Hz, 1H), 8.25 (dt, $J = 7.8, 1.1$ Hz, 1H), 8.06 – 7.98 (m, 1H), 7.84 (td, $J = 7.7, 1.7$ Hz, 1H), 7.40 – 7.35 (m, 2H), 7.32 (td, $J = 7.8, 1.4$ Hz, 1H), 7.28 – 7.19 (m, 1H), 7.24 – 7.12 (m, 1H), 6.78 – 6.68 (m, 2H), 4.95 (td, $J = 10.9, 4.4$ Hz, 1H), 2.21 – 2.11 (m, 1H), 2.09 – 1.99 (m, 1H), 1.74 (d, $J = 11.4$ Hz, 2H), 1.62 – 1.51 (m, 2H), 1.15 (q, $J = 13.7, 12.5$ Hz, 2H), 0.98 – 0.90 (m, 7H), 0.82 (d, $J = 6.9$ Hz, 3H). $^{13}\text{C NMR}\{^1\text{H}\}$ (101 MHz, CDCl_3) δ 162.3, 150.0, 149.5, 148.1, 137.5, 134.5, 134.2, 131.4, 130.7, 126.9, 126.7, 126.3, 124.7, 122.3, 121.1, 117.3, 114.4, 112.7, 74.7, 47.3, 41.2, 34.4, 31.6, 26.7, 23.7, 22.2, 20.9, 16.7.

(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)benzoate (154)

2-(2-(pyridin-2-yl)-1*H*-benzo[*d*]imidazol-1-yl)



155 (245 mg, 0.5 mmol, 1 eq) was dissolved in dioxane (5 mL) and $\text{BF}_3 \cdot \text{OEt}_2$ (183 μL , 1.3 mmol, 2.5 eq) and the reaction mixture was refluxed for 18 hours. After 18 hours, 10% aq. K_2CO_3 (5 mL) and water (5 mL) were added. The resulting solution was extracted with DCM (3x 10 mL). Combined organic extracts were dried with MgSO_4 , evaporated and purified by column chromatography (hexane: EtOAc 4:1) to yield 180 mg of product as oil (80%). Isolated as a mixture of diastereomers in 1.25:1 ratio. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.35 (dq, $J = 8.0, 1.0$ Hz, 1H), 8.32 (dq, $J = 8.0, 1.0$ Hz, 1H), 8.27 – 8.11 (m, 4H), 7.93 – 7.84 (m, 2H), 7.76 – 7.52 (m, 7H), 7.47 – 7.39 (m, 1H), 7.44 – 7.35 (m, 1H), 7.36 – 7.25 (m, 2H), 7.28 – 7.15 (m, 2H), 7.19 – 7.07 (m, 2H), 7.02 – 6.93 (m, 1H), 6.97 – 6.88 (m, 1H), 4.53 – 4.38 (m, 2H), 1.53 – 1.33 (m, 6H), 1.32 – 1.08 (m, 5H), 0.93 – 0.75 (m, 5H), 0.69 (d, $J = 6.5$ Hz, 4H), 0.62 (d, $J = 6.4$ Hz, 3H), 0.49 (d, $J = 7.0$ Hz, 4H), 0.44 (d, $J = 6.9$ Hz, 3H), 0.40 – 0.33 (m, 7H), -0.29 (q, $J = 12.6$ Hz, 1H). $^{13}\text{C NMR}\{^1\text{H}\}$ (101 MHz, CDCl_3) δ 165.1, 164.9, 150.4, 149.6, 148.6, 148.5, 142.8, 142.6, 138.8, 138.7, 138.2, 138.0, 136.3, 132.9, 132.8, 132.1, 131.8, 130.1, 129.9, 129.7, 128.7, 123.9, 123.9, 123.6, 123.5, 123.0, 120.0, 110.8, 110.7, 75.0, 74.9, 46.4, 46.2, 39.8, 39.2, 34.0, 33.9, 31.2, 31.0, 25.6, 25.4, 22.8, 21.9, 20.7, 15.8, 15.7.

GENERAL PROCEDURE FOR SYNTHESIS OF KETIMINES 156-161

Ketone (5 mmol) was dissolved in toluene (50 ml) and aniline (5 mmol) was added followed by pTSA (50 mg) and molecular sieves. This mixture was stirred at room temperature for 24 hours. Afterwards, the reaction was filtered and the solvent was evaporated. Crude product was purified by recrystallization from diethyl ether.

1-(4-bromophenyl)-*N*-(4-methoxyphenyl)ethan-1-imine (156)

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.87 – 7.80 (m, 2H), 7.61 – 7.54 (m, 2H), 6.95 – 6.88 (m, 2H), 6.80 – 6.71 (m, 2H), 3.82 (s, 3H), 2.24 (s, 3H). $^{13}\text{C NMR}\{^1\text{H}\}$ (101 MHz, CDCl_3) δ 164.8, 156.3, 144.4, 138.6, 131.6, 128.9, 125.1, 120.9, 114.4, 55.6, 17.3.

***N*-1-bis(4-methoxyphenyl)ethan-1-imine (158)**

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.99 – 7.88 (m, 2H), 7.00 – 6.89 (m, 2H), 6.95 – 6.85 (m, 2H), 6.79 – 6.69 (m, 2H), 3.87 (s, 3H), 3.82 (s, 3H), 2.22 (s, 3H). $^{13}\text{C NMR}\{^1\text{H}\}$ (101 MHz, CDCl_3) δ 164.9, 161.6, 155.9, 145.2, 132.6, 128.9, 121.0, 114.4, 113.7, 55.6, 55.5, 17.2.

***N*-(4-methoxyphenyl)-1-(4-nitrophenyl)ethan-1-imine (159)**

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.31 – 8.26 (m, 2H), 8.15 – 8.11 (m, 2H), 6.96 – 6.92 (m, 2H), 6.80 – 6.75 (m, 2H), 3.83 (s, 3H), 2.32 (s, 3H). $^{13}\text{C NMR}\{^1\text{H}\}$ (101 MHz, CDCl_3) δ 196.8, 156.7, 145.5, 144.0, 128.2, 123.7, 120.9, 114.5, 55.7, 17.6.

1-(4-bromophenyl)-*N*-(3,5-dimethylphenyl)ethan-1-imine (160)

¹H NMR (400 MHz, CDCl₃) δ 7.85 – 7.83 (m, 0H), 7.82 – 7.81 (m, 1H), 7.61 – 7.54 (m, 1H), 7.56 – 7.54 (m, 1H), 6.73 (tt, *J* = 1.5, 0.7 Hz, 1H), 6.41 – 6.39 (m, 2H), 2.31 (t, *J* = 0.9 Hz, 6H), 2.21 (s, 3H). ¹³C NMR{¹H} (101 MHz, CDCl₃) δ 164.0, 151.5, 138.8, 138.6, 131.6, 128.9, 125.2, 125.1, 117.0, 21.5, 17.3.

1-(4-bromophenyl)-*N*-(naphthalen-1-yl)ethan-1-imine (161)

¹H NMR (400 MHz, CDCl₃) δ 8.01 – 7.96 (m, 2H), 7.88 – 7.84 (m, 1H), 7.75 – 7.71 (m, 1H), 7.65 – 7.60 (m, 3H), 7.52 – 7.39 (m, 3H), 6.77 (dd, *J* = 7.2, 1.1 Hz, 1H), 2.19 (s, 3H). ¹³C NMR{¹H} (101 MHz, CDCl₃) δ 165.5, 147.8, 138.3, 134.4, 131.8, 129.1, 128.2, 126.3, 126.0, 126.0, 125.6, 125.5, 123.6, 123.6, 113.5, 17.7.

3-phenyl-2*H*-benzo[*b*][1,4]oxazine (162)

2-aminophenol (109 mg, 1 mmol, 1 eq) was dissolved in DCM (20 mL). Then, 20% aq. K₂CO₃ (20 mL) was added followed by nBu₄NHSO₄ (17 mg, 0.05 mmol, 0.05 eq) and bromoacetophenone (200 mg, 1 mmol, 1 eq). The reaction was stirred at room temperature for 18 hours. After 18 hours, the layers were separated, and the organic layer was evaporated. The residue was purified by column chromatography (Hexane: EtOAc 10:1) to yield 126 mg of light solid (60%). ¹H NMR (400 MHz, CDCl₃) δ 7.95 – 7.90 (m, 2H), 7.51 – 7.46 (m, 3H), 7.44 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.15 (ddd, *J* = 7.9, 7.4, 1.7 Hz, 1H), 7.03 (td, *J* = 7.6, 1.4 Hz, 1H), 6.92 (dd, *J* = 7.9, 1.4 Hz, 1H), 5.08 (s, 2H). ¹³C NMR{¹H} (101 MHz, CDCl₃) δ 158.8, 146.5, 135.6, 133.9, 131.3, 129.6, 128.9, 128.8, 128.5, 128.0, 126.6, 122.5, 115.7, 63.1.

3-phenylquinoxalin-2(1*H*)-one (163)

Methyl benzylformate (164 mg, 1 mmol, 1 eq) was dissolved in THF (9 mL) and pyridine (1 mL). Benzene-1,2-diamine (108 mg, 1 mmol, 1 eq) was added and the mixture was refluxed for 90 minutes. After 90 minutes, the reaction mixture was cooled to room temperature, evaporated and the residue was suspended in diethyl ether. The suspension was filtered and dried. Isolated 160 mg (72%).

¹H NMR (400 MHz, DMSO-*D*₆) δ 12.56 (s, 1H), 8.36 – 8.26 (m, 2H), 7.87 – 7.81 (m, 1H), 7.59 – 7.46 (m, 4H), 7.37 – 7.31 (m, 2H). ¹³C NMR{¹H} (101 MHz, CDCl₃) δ 158.8, 146.5, 135.6, 133.9, 131.3, 129.6, 128.9, 128.8, 128.0, 126.6, 122.5, 116.3, 115.7, 63.1.

GENERAL PROCEDURE FOR REDUCTION OF KETIMINES

Reduction with racemic ligand to provide racemic mixture as a reference for chiral SFC

Ketimine (0.115 mmol, 1 eq) was dissolved in chloroform (1 mL) and ligand (0.023 mmol, 0.2 eq) was added. To this solution, trichlorosilane (34 μL, 0.45 mmol, 3 eq) and the reaction was stirred at room temperature for 18 hours. After 18 hours, sat. NaHCO₃ solution (1 mL) was added, and the biphasic system was shaken. The resulting gel-like precipitate was filtered, and the organic layer was separated. The aqueous layer was extracted with EtOAc (2x 2 mL). Organic extracts were combined, washed with brine, dried with MgSO₄ and evaporated. The residue was purified by column chromatography.

Reduction with chiral ligand

Ketimine (0.115 mmol, 1 eq) was dissolved in dry toluene (1 mL) and ligand (0.001 mmol, 0.01 eq as a toluene solution with such concentration to add between 50-100 μL of the solution) was added. To this solution, trichlorosilane (34 μL, 0.45 mmol, 3 eq) and the reaction was stirred at room temperature for 18 hours. After 18 hours, sat. NaHCO₃ solution (1 mL) was added, and the biphasic system was shaken. The resulting gel-like precipitate was filtered, and the organic layer was separated. The aqueous layer was extracted with EtOAc (2x 2 mL). Organic extracts were combined, washed with brine, dried with MgSO₄ and evaporated. The residue was purified by column chromatography.

***N*-(1-(4-bromophenyl)ethyl)-4-methoxyaniline (157)**

¹H NMR (400 MHz, CDCl₃) δ 7.45 – 7.40 (m, 2H), 7.26 – 7.22 (m, 2H), 6.72 – 6.66 (m, 2H), 6.46 – 6.39 (m, 2H), 4.36 (q, *J* = 6.7 Hz, 1H), 3.70 (s, 3H), 1.47 (d, *J* = 6.8 Hz, 3H). ¹³C NMR {¹H} (101 MHz, CDCl₃) δ 152.3, 144.8, 141.3, 131.9, 127.9, 120.6, 114.9, 114.8, 55.9, 54.0, 25.2.

4-methoxy-*N*-(1-(4-methoxyphenyl)ethyl)aniline (reduction of imine 158)

¹H NMR (400 MHz, CDCl₃) δ 8.20 – 8.16 (m, 2H), 7.56 – 7.52 (m, 2H), 6.71 – 6.66 (m, 2H), 6.43 – 6.38 (m, 2H), 4.50 (q, *J* = 6.7 Hz, 1H), 3.82 (s, 3H), 3.69 (s, 3H), 1.52 (d, *J* = 6.8 Hz, 3H). ¹³C NMR {¹H} (101 MHz, CDCl₃) δ 153.6, 152.5, 147.2, 140.8, 126.9, 124.2, 115.0, 114.7, 55.8, 54.2, 25.1.

4-methoxy-*N*-(1-(4-nitrophenyl)ethyl)aniline (reduction of imine 159)

¹H NMR (400 MHz, CDCl₃) δ 7.31 – 7.27 (m, 2H), 7.11 (d, *J* = 9.0 Hz, 2H), 6.79 – 6.75 (m, 2H), 6.68 – 6.64 (m, 2H), 4.40 (q, *J* = 6.9 Hz, 1H), 3.75 (s, 3H), 3.71 (s, 3H), 1.84 (d, *J* = 6.9 Hz, 3H). ¹³C NMR {¹H} (101 MHz, CDCl₃) δ 196.81, 156.70, 145.46, 143.97, 128.21, 123.69, 120.91, 114.52, 77.16, 55.66, 17.60.

3-phenyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (reduction of imine 162)

¹H NMR (400 MHz, CDCl₃) δ 7.44 – 7.32 (m, 5H), 6.88 – 6.80 (m, 2H), 6.71 (ddd, *J* = 15.7, 7.8, 1.6 Hz, 2H), 4.52 (dd, *J* = 8.6, 3.0 Hz, 1H), 4.30 (dd, *J* = 10.6, 3.0 Hz, 1H), 4.01 (dd, *J* = 10.6, 8.6 Hz, 1H). ¹³C NMR {¹H} (101 MHz, CDCl₃) δ 143.7, 139.3, 134.0, 129.0, 128.5, 127.3, 121.6, 119.1, 116.7, 115.5, 71.1, 54.4.

3-phenyl-3,4-dihydroquinoxalin-2(1*H*)-one (reduction of imine 163 only with racemic ligand)

¹H NMR (400 MHz, DMSO-*D*₆) δ 10.39 (s, 1H), 7.35 – 7.30 (m, 4H), 7.28 – 7.24 (m, 1H), 6.81 – 6.75 (m, 2H), 6.75 – 6.71 (m, 1H), 6.64 (s, 1H), 6.59 (ddd, *J* = 7.8, 6.2, 2.5 Hz, 1H), 4.92 (s, 1H). ¹³C NMR {¹H} (101 MHz, DMSO-*D*₆) δ 165.8, 140.3, 133.8, 128.3, 127.5, 126.9, 123.0, 117.6, 114.7, 113.3, 59.3.

7. List of author's publications

- 1 **Kriegelstein, M.**; Profous, D.; Lyčka, A.; Trávníček, Z.; Příbylka, A.; Volná, T.; Benická, S.; Cankař, P. Axially Chiral Trifluoromethylbenzimidazolylbenzoic Acid: A Chiral Derivatizing Agent for α -Chiral Primary Amines and Secondary Alcohols to Determine Absolute Configuration. *J. Org. Chem.* **2019**, *84* (18), 11911–11921.
- 2 **Kriegelstein, M.**; Profous, D.; Příbylka, A.; Cankař, P. The Assignment of Absolute Configuration of β -Chiral Primary Alcohols with Axially Chiral Trifluoromethylbenzimidazolylbenzoic Acid. *J. Org. Chem.* **2020**, *85* (20), 1–10.
- 3 **Kriegelstein, M.**; Profous, D.; Příbylka, A.; Lyčka, A.; Cankař, P. Limitations of Trifluoromethylbenzoimidazolylbenzoic Acid as a Chiral Derivatizing Agent to Assign Absolute Configuration for β - Chiral Aminoalcohols. *ACS Omega* **2022**, *7* (15), 12734–12746.

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