University of Pardubice

Faculty of Chemical Technology

Utilization of α-amino acids in the synthesis of nitrogen heterocycles

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Doctoral Thesis

2016

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V Pardubicích dne 7. 11. 2016 Pravinkumar Hansraj Mohite

Dedicated to my beloved parents

and specialy to my wife Pallavi,

who have been my inspiration throughout.

And to all who have been with me, beside me,

all through my life.

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I would like to express my heartfelt gratitude towards my supervisor, Assoc. Prof. Filip Bureš Ph.D., whose knowledge and vast experience has inspired me at every stage of my tenure and helped me to achieve this target. I will be always obliged to him for his suggestions, criticisms and constant encouragement. I would not have imagined a better advisor and mentor for my Ph. D. study.

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The single largest contribution in shaping my present comes from the faith, hope, encouragement and affection of my beloved parents mother Rajani & father Hansraj and wife Pallavi. The debt of gratitude I owe them is beyond literal expression hence I make no effort. Special thanks to my Late Grandfather for his blessings. The love and affection showered by my sister kiran on me is magnanimous. I thank my baby daughter “Awani” for making my life more beautiful. I am very thankful to my uncle, aunty, Kajal and Shubham for their belief in my abilities and constant encouragement. My heart felt regard goes to my father in law, mother in law, Vishal and Pawan for their love and moral support.

ANNOTATION

This doctoral work focuses on introduction of α-amino acid pendants on five membered nitrogen heterocyclic compounds. The literature search has mainly been focused on benzo[*d*]imidazole and benzo[*d*]oxazole derivatives. In the experimental part, several new benzo[*d*]imidazole derivatives bearing α-amino acid residues attached at the C2 position were designed and prepared. These optically pure primary amines were further applied as organocatalysts in asymmetric aldol reactions.

KEYWORDS

benzo[*d*]imidazole, α-amino acid, amine, aldol reaction, organocatalysis

NÁZEV

Využití α-aminokyselin v syntéze dusíkatých heterocyklů

ANOTACE

Práce se zaměřuje na zavedení zbytku α-aminokyseliny do struktury pětičlenných dusíkatých heterocyklických sloučenin. Rešeršní část se zaměřila především na deriváty benzo[*d*]imidazolu a benzo[*d*]oxazolu. V experimentální části bylo navrženo a připraveno několik nových derivátů benzo[*d*]imidazolu nesoucích zbytek α-aminokyseliny připojený v poloze C2. Tyto opticky čisté primární aminy byly dále využity jako organokatalyzátory v asymetrických aldolových reakcích.

KLÍČOVÁ SLOVA

benzo[*d*]imidazol, α-aminokyselina, amin, aldolová reakce, organokatalýza

Contents

List of abbreviations

AcOH	acetic acid
Ala	2-aminopropanoic acid
BINAP	(2, 2'-bis(diphenylphosphino)-1,1'-binapthyl)
Bn	benzyl
Boc, BOC	*t*-butoxycarbonyl
Cbz , Z	benzyloxycarbonyl
DCC	*N*,*N'*-dicyclohexylcarbodiimide
DCM	dichloromethane
DHB	2,5-dihydroxybenzoic acid
DIAD	di*iso*propyl azodicarboxylate
DMF	dimethylformamide
EDC	ethylene dichloride
EtOAC	ethyl acetate
FRET	fluorescence resonance energy transfer
HATR	horizontal attenuated total reflectance
HoBt	hydroxybenzotriazole
Ile	2-amino-3-methylpentanoic acid
*i*Pr	*iso*propyl
IR	infrared
Leu	2-amino-4-methylpentanoic acid
LiHMDS	lithium hexamethyldiSilazide
LTA	lipoteichoic acid
Me	methyl
Phe	2-amino-3-phenylpropanoic acid
R_f	retention factor
TEA	triethylamine
TFA	trifluoroacetic acid

THF	tetrahydrofuran
Trp	2-amino-3-(1*H*-indol-3-yl)propanoic acid
S/C	substrate to catalyst ratio
Val	2-amino-3-methylbutanoic acid

O. Introduction and aims of the work

α-Amino acids represent unique class of organic molecules with a wide natural abundance. Many of the α-amino acids are considered as essential and are prerequisite for genesis of life. These molecules contain one or more asymmetric centers and their combination with a suitable heteroaromatic compounds would render very interesting optically active substances. In general, such molecules possess biological activity and can be used in pharmacy, as nitrogen ligands capable of coordinating various (transition) metals as well as organocatalysts. Hence, in this doctoral work a particular emphasis is put on essential α-amino acids such as Ala, Val, Phe, Leu, iLe, Trp and their use as readily available and inexpensive starting materials (chiral pool) for the construction of five membered heterocyclic compounds such as imidazole. Optically active imidazole derivatives have a long tradition in our working group and, therefore, I attempted to further extend this topic.

The ***principal aims*** of my doctoral thesis are as follow:

1. To perform a literature search focusing on utilization of α-amino acids in the construction of benzo[*d*]imidazole and benzo[*d*]oxazole derivatives.
2. Based on these outcomes, to design new class of imidazole derivatives to be prepared.
3. To convert readily available α-amino acids into target imidazole derivatives bearing free amino group.
4. To further apply successfully prepared optically pure amines as catalysts or ligands in selected asymmetric reactions.

1. Structure and properties of benzo[*d*]midazole and benzo[*d*]oxazole

Parent benzo[*d*]imidazole and benzo[*d*]oxazole represent heteroaromatic chemical compounds which share a fundamental structural features of six-membered benzene fused to five-membered imidazole or oxazole (*Figure 1*). The other, most commonly used chemical names of these two compounds appearing in the literature are benzimidazole, 1*H*-benzimidazole and benzoxazole.

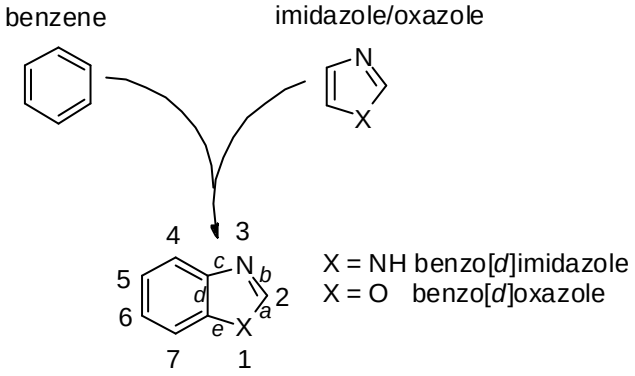


Figure 1. *Fusion of benzene ring with imidazole or oxazole leads to benzo[d]imidazole and benzo[d]oxazole.*

Benzo[*d*]imidazole is a white to slightly beige solid which melts at 172 °C and boils at 360 °C. It is slightly soluble in water and well soluble in alcohols. It is a bicyclic compound having imidazole ring (containing two nitrogen atoms at nonadjacent positions) fused to benzene. Benzo[*d*]imidazolium ion has *pKa* = 5.68, whereas *pKa* of the proton ionization of the *N*-unsubstituted benzo[*d*]imidazole is 12.75. Thus, benzo[*d*]imidazole is stronger NH-acid than parent 1*H*-imidazole (*pKa* = 14.4).[1] Benzo[*d*]imidazoles which contain a hydrogen atom attached at the N1-position readily undergo tautomerization (*Figure 2*).[2] Acid character, H-bonding and possible tautomerization also account for the generation of benzo[*d*]imidazole aggregates and clusters (either in solution or solid state).

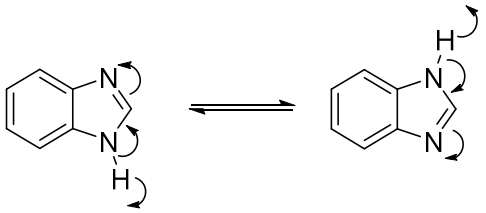


Figure 2. *Benzo[d]imidazole tautomerisation.*

In benzo-condensed systems, electrophilic aromatic substitution occurs on the benzene ring as well as on the five-membered heterocycle. Principal reactions and

selectivity of benzo[*d*]imidazole and benzo[*d*]oxazole with electrophiles E and nucleophiles Nu can be summarized as shown in *Figure 3*.

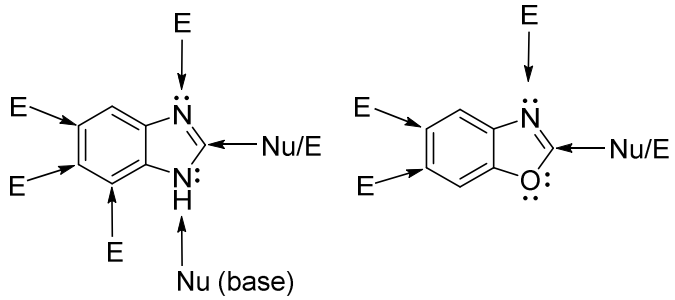
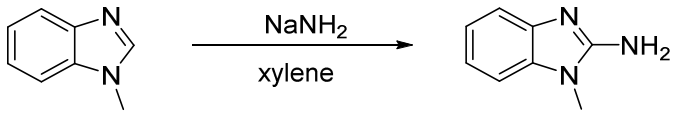


Figure 3. *Principal reactivity with electrophiles and nucleophiles.*

Electrophiles may attack either heteroatoms of the heterocycle bearing lone electron pairs, C2-position or the fused benzene ring. In benzo[*d*]imidazole, the proton at N1 can be abstracted by a base. Nucleophiles react faster with N1-substituted benzo[*d*]imidazoles than with imidazoles, the attack occurs at the C2-position. For instance, treatment of 1-methylbenzo[*d*]imidazole with sodium amide in xylene gives the corresponding 2-amino-1-methylbenzo[*d*]imidazole (*Scheme 1*).[3]



Scheme 1. *Nucleophilic attack on the C2-postion of benzo[d]imidazole.*

The most prominent benzo[*d*]imidazole derived compound in the nature is *N*-ribosyldimethylbenzo[*d*]midazole (alpha-ribazole, *Figure 4*), which serves as an axial ligand for cobalt in vitamin B_{12}.[1] However, benzo[*d*]imidazole is also a part of many medicinally active substances.[4]

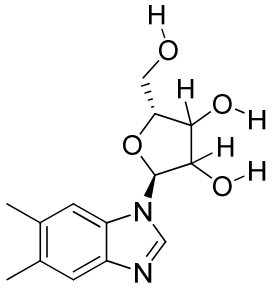
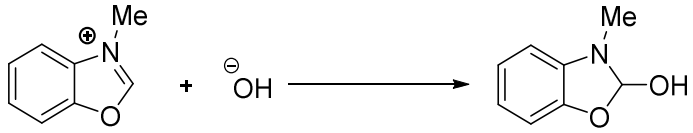


Figure 4. *N-Ribosyldimethylbenzo[d]imidazole (alpha-ribazole).*

Benzo[*d*]imidazole, in an extension to well-elaborated imidazole system, has been used as carbon scaffold for *N*-heterocyclic carbenes (NHC). The NHC's are usually used as ligands for transition metal complexes. They are often prepared by deprotonation of *N*,*N'*-disubstituted benzo[*d*]imidazolium salt at the C2-position using a strong base.[5,6]

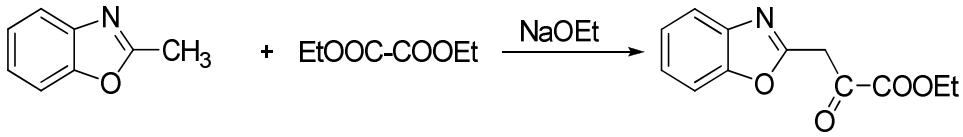
Benzo[*d*]imidazoles are clearly powerful chemical species with a wide range of applications and also great untapped potential. Combining reactivity and modularity, benzo[*d*]imidazole represents undoubtedly a unique scaffold.

Benzo[*d*]oxazole forms colorless crystals with mp and bp of 27-30 and 182 ºC, respectively. Benzo[*d*]oxazole undergoes electrophilic aromatic attack at the positions C4 and C5 (*Figure 3*), for instance nitration of benzo[*d*]oxazole leads to 5- or 6-nitrobenzo[*d*]oxazole. However, nucleophilic attack of benzo[*d*]oxazoles and benzo[*d*]oxazolium salts takes place at the C2-position in terms of nucleophilic addition (*Scheme 2*).[3]



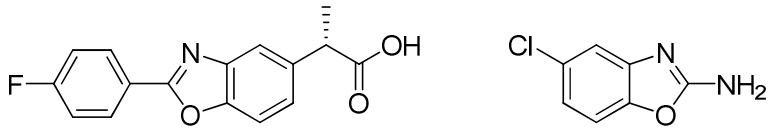
Scheme 2. *Nucleophilic attack at the C2-postion of benzo[d]xazolium.*

Hydrogen from the benzylic 2-alkylbenzo[*d*]oxazoles can be abstracted by a base and, therefore, 2-methylbenzoxazole undergoes for instance Claisen condensation (*Scheme 3*).[3]



Scheme 3*.Claisen condensation of 2-methylbenzoxazole.*

Benzo[*d*]oxazoles are privileged organic compounds of great medicinal significance, found in many natural compounds and are widely employed in drug discovery program.[7] Being a heterocyclic compound, benzo[*d*]oxazole found use as starting material for the synthesis of larger, usually bioactive structures. For instance, it can be found incorporated in many pharmaceutical drugs such as flunoxaprofen and zoxazolamine (*Figure 5*).



Flunoxaprofen Zoxazolamine

Figure 5. *Structure of flunoxaprofen and zoxazolamine drugs.*

Apart from the bioactive molecules, benzo[*d*]oxazole derivatives have also been used as ligands in organometallic systems and in dyes with semiconducting properties. Absorption and steady-state fluorescence of halogenated derivatives of benzo[*d*]oxazole were studied in solution as well as in solid state.[8]

2. Amino acids-basic introduction

Amino acids are a type of organic acids that contain both carboxyl group (COOH) and amino group (NH_2). The general formula of α-amino acid is given below (*Figure 6*) in which the R denotes an organic substituent known as a "side-chain".

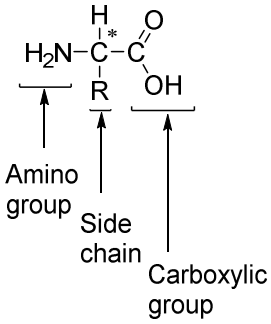
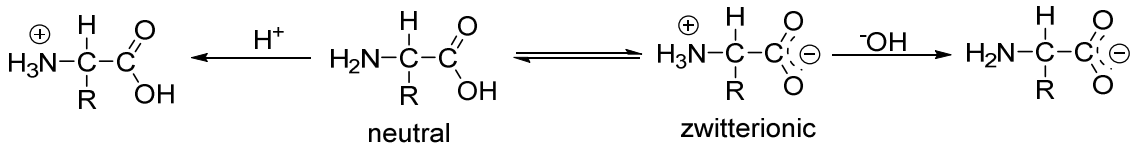


Figure 6. *α-Amino acid - general structure.*

Although the neutrally-charged structure is commonly written, it is inaccurate because both acidic COOH and basic NH_2 groups may mutually transfer H^+ ion. Hence, amino acids may exist as neutral or zwitterion structures (both with overall zero charge) and as such are sparingly soluble in water. However, placing the amino acid to an acid or alkaline media results in its dissolution caused either by NH_2-protonation or COOH-deprotonation (*Scheme 4*). Thus, each particular amino acid possesses a pH of the isoelectric point at which is in neutral/zwitterionic form (insoluble).



Scheme 4. *Acid-base properties of amino acids.*

Other very important and dominant features especially of α-amino acids are the presence of a stereogenic center and natural occurrence. Hence, naturally occurring α-amino acids are generally considered as a readily accessible chiral pool for organic synthesis. In this respect, introduction of chiral centers with the given absolute configuration (optical purity) into a desired molecule is accomplished directly from the starting amino acid and not solely by asymmetric synthesis.[9] Nowadays, optically pure α-amino acids are commonly available commercial compounds and besides the naturally occurring and very inexpensive

L-amino acids [all (*S*)-amino acids except cysteine], corresponding D-enantiomers [all (*R*)-amino acids except cysteine] began to be also supplied for a reasonable price (*Figure 7*).

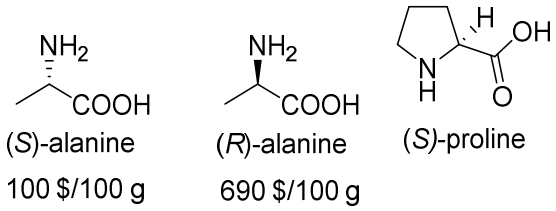


Figure 7. *Configuration and average prices for (S)- and (R)-alanine enantiomers and structure of proline.*

From the asymmetric catalysis point of view, proline can be considered as the most successfully and widely applied α-amino acid (*Figure 7*). Proline itself may organocatalyze plenty of asymmetric reactions such as aldol, Mannich and Michael reactions as well as reductions.[10] The main reasons of such "proline popularity" can be seen in its chemical structure. In contrast to other essential α-amino acids, proline possesses secondary amine which, in conjunction with the carboxylic acid, may behave as bifunctional asymmetric catalyst and thus resembles some natural enzymes. It is also chiral bidentate ligand that forms stable and catalytically active metal complexes.

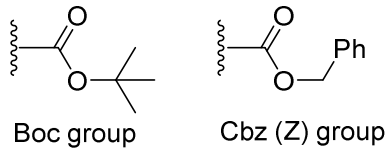


Figure 8. *Boc and Cbz (Z) protecting groups.*

However, amino acids themselves do not undergo standard chemical transformation which is mainly given by their acid/base character and poor solubility in common organic solvents. Hence, it is often necessary to protect either one or both reactive functionalities (the amine and carboxylic acid groups). The carboxylic acid group can easily be converted to an ester by standard esterification techniques. The amine must be protected with a group that can withstand a wide range of chemical manipulations and yet should also be easily removable under mild conditions. Two such groups that have emerged as versatile protective functionalities are the *t*-butoxycarbonyl (Boc) and benzyloxycarbonyl (Cbz, Z) groups (*Figure 8*). The Boc group is able to withstand catalytic hydrogenation, sodium in liquid ammonia, alkali, and hydrazine[11] but is rapidly cleaved under mild acid conditions, usually by

trifluoroacetic acid. On the other hand, the Cbz group is relatively stable towards acidic conditions but is easily removed by catalytic hydrogenation. Moreover, all of the common α-amino acids are commercially available in their Boc- or Cbz-protected forms.

3. Benzo[*d*]imidazoles and benzo[*d*]oxazoles bearing an α-amino acid residue

An integration of the aforementioned two types of organic compounds would render a heterocyclic compound bearing chiral residue. Such molecules combine all aspects of benzo-fused heterocycles and α-amino acids. Thus, due to the presence of a stereogenic center they are optically active (pure), possess acid-base and chelating ability, may (not) undergo tautomerism and gain biological activity and improved solubility. In the working group of F. Bureš, several imidazole derivatives linked to an α-amino residue were developed within the last several years (*Figure 9*).[12–20] Derivatives **1**–**10** were more or less successfully applied as optically active nitrogen ligands in various asymmetric reactions, as ionic liquids, novel macrocyclic imidazoliophanes or biologically active compounds.

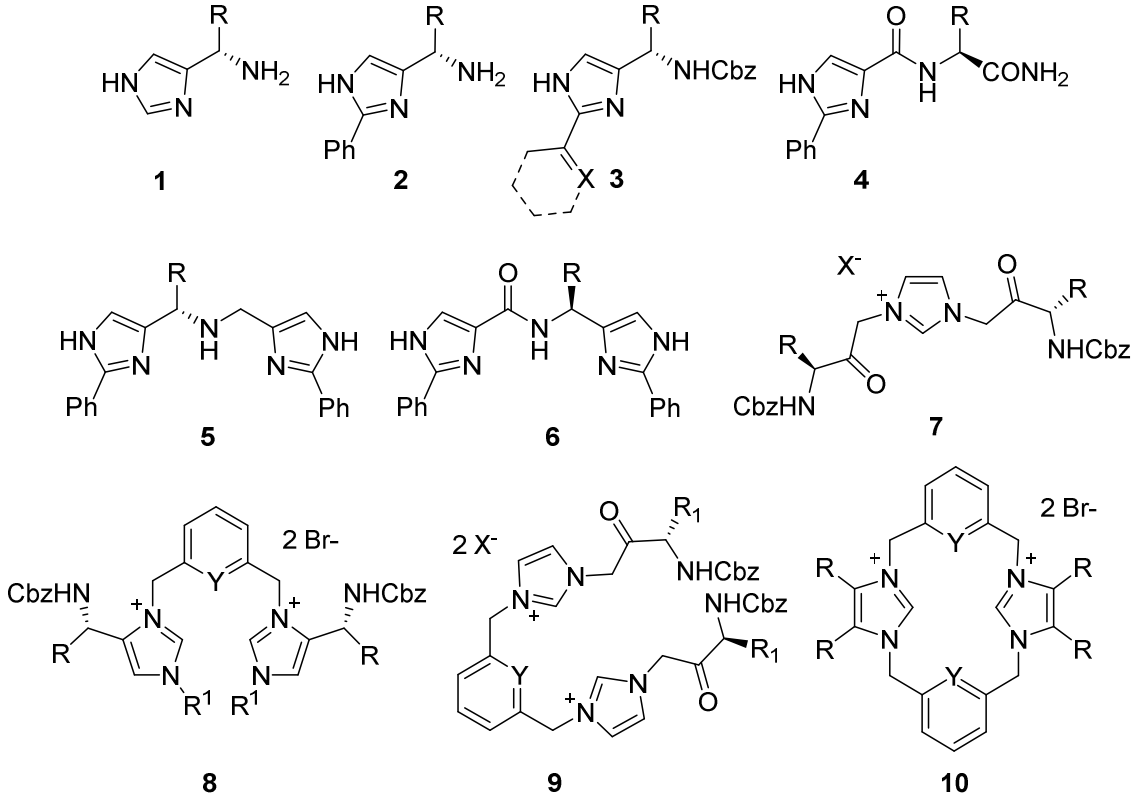


Figure 9. *Imidazole derivatives linked to an α-amino acid residue – an overview.*

The joint features of molecules **1**–**10** are: i) the presence of solely 1*H*-imidazol ring and ii) α-amino acid pendants appended solely at imidazole C4 and C5, respectively. Hence, taking these molecules as a starting point of my doctoral studies, new benzo[*d*]imidazole and their isolobal analogues - benzo[*d*]oxazole derivatives bearing an α-amino acid residue were envisaged (*Figure 10*). In contrast to **1**–**10**, the newly proposed compounds utilize benzene-fused imidazole as a parent scaffold and α-amino acid pendants (R) principally connected at the position C2 between both nitrogen atoms.

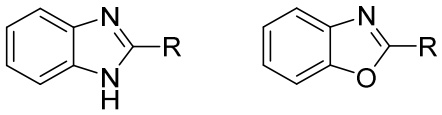
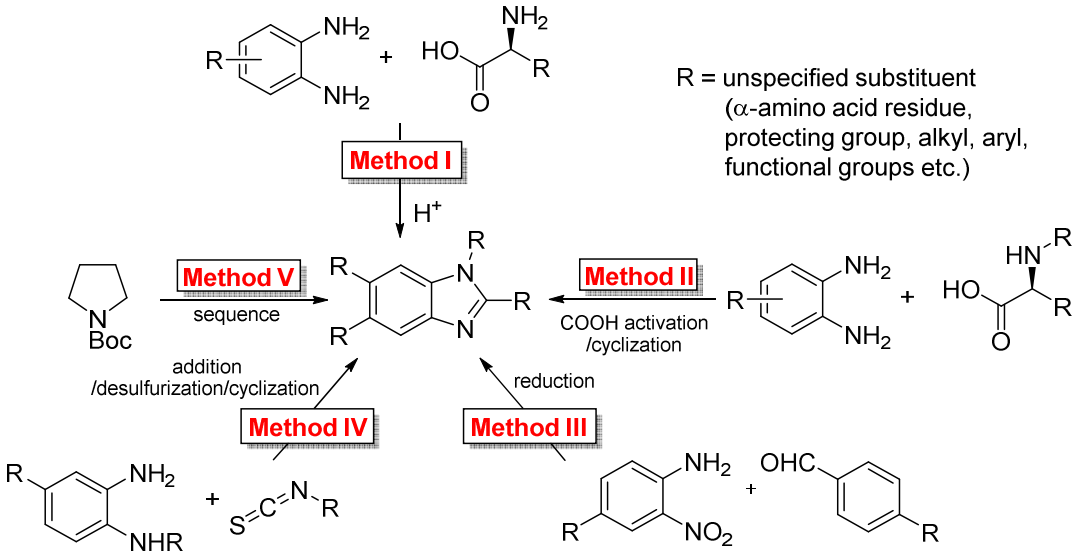


Figure 10. *Newly proposed benzo[d]imidazole and benzo[d]oxazole derivatives with α-amino acid residue (R) attached at position C2.*

Hence, based on this proposal I will focus further literature search towards synthetic pathways to benzo[*d*]imidazoles and benzo[*d*]oxazoles and, subsequently, to prospective applications of such compounds.

4. Synthetic approaches leading to benzo[*d*]imidazoles



Scheme 5. *The general synthetic approaches to benzo[d]imidazole bearing α-amino acid residue.*

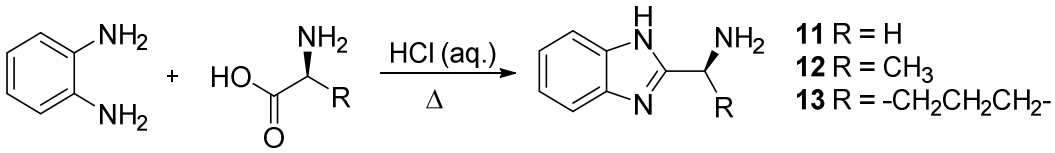
From the synthetic point of view, the most likely expected orientation of the α-amino acid substituent is at the C2 involving the carboxylic acid in the construction of imidazole ring. *Scheme 5* summarizes the methods currently available in the literature used for the construction

of the aforementioned benzo[*d*]imidazole derivatives. The methods can be divided in five categories according to the starting material used, methodology or type of the derivatives prepared. In the subsequent text will be discussed each particular method I-V according to *Scheme 5*.

4.1 Method I

Benzene-1,2-diamine (*o*-phenylenediamine) represents the most widely employed starting material used for the construction of benzo[*d*]imidazoles. Its direct treatment with α-amino acid results in formation of C2-substituted derivatives. This reaction was for instance used by Barot *et al.* (*Scheme 6*).[21] They heated glycine with *o*-phenylenediamine in aqueous HCl at 70 °C for one hour to afford 2-aminomethylbenzo[*d*]imidazole **11** in 71% yield.

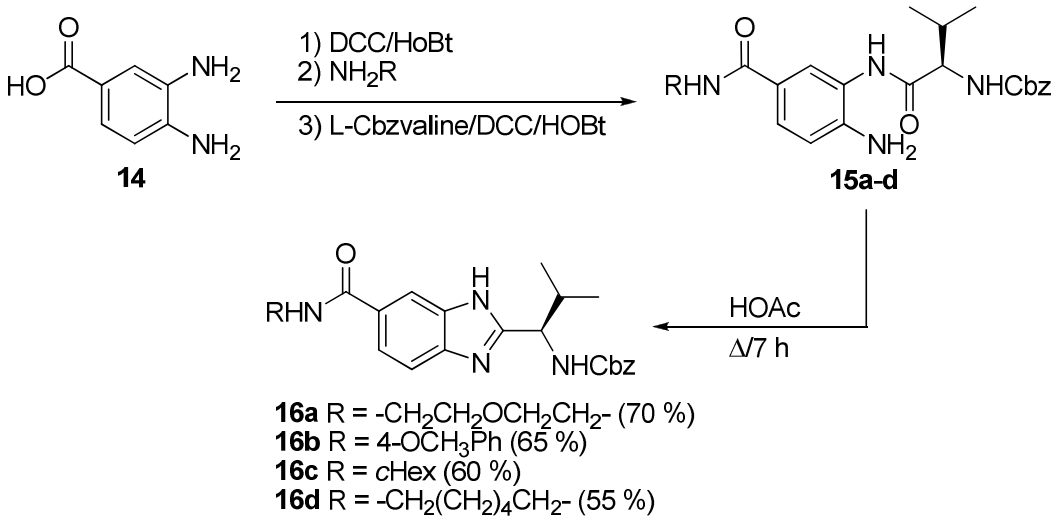
Xu *et al.* also carried out similar reaction with L-alanine and L-proline.[22] The reaction was catalyzed by 5M HCl and afforded compounds **12** and **13** in poor yields of 32 and 51 %. Hence, although is this reaction operationally very easy, the attained yields are generally low.



Scheme 6. *Direct heating of the α-amino acid with benzene-1,2-diamine.*

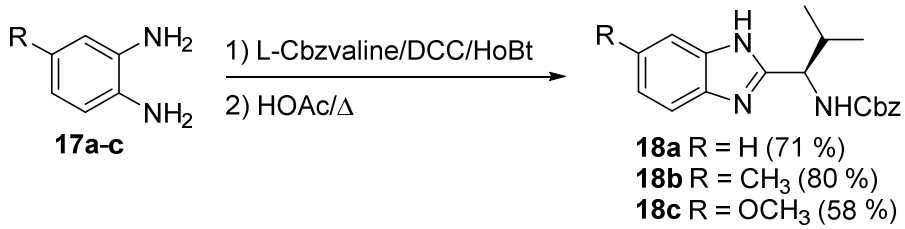
4.2 Method II

The second method involves also benzene-1,2-diamine as a source of fused benzene ring and imidazole nitrogens. However, the carboxylic function of the protected α-amino acid is firstly activated and then treated with *o*-phenylenediamine (*Scheme 7*).[23] The protocol of Zhang involves pre-amidation of 3,4-diaminobenzenecarboxylic acid **14** and reaction with DCC/HoBt-activated Cbz-protected L-valine to afford monoamides **15a**–**d**. The cyclization to benzo[*d*]imidazoles **16a**–**d** has been accomplished *via* heating in acetic acid. The yield of target derivatives **16a**–**d** ranges from 55 to 70 %.



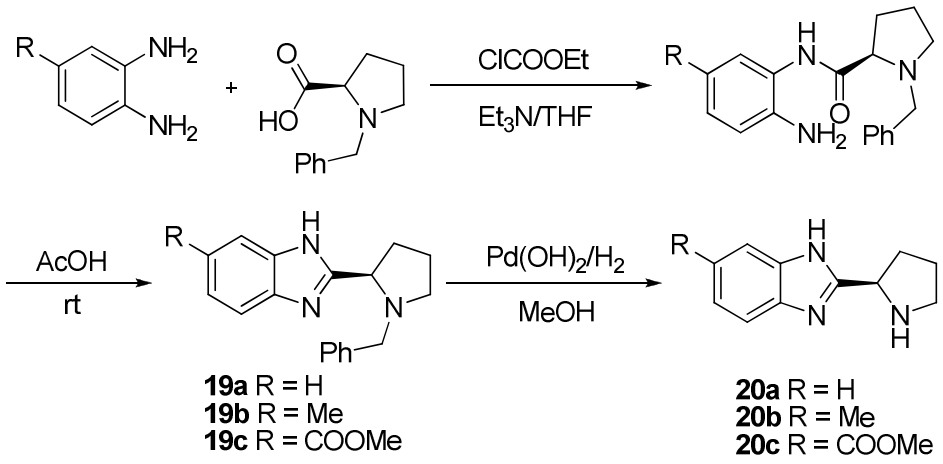
Scheme 7. *Activation of the carboxylic function, amidation and cyclization.*

Very similar reaction with L-Cbzvaline has also been carried out with substituted *o*-phenylenediamines **17** resulting in a series of novel derivatives **18a**–**c** (*Scheme 8*).[23]



Scheme 8. *Substituted o-phenylenediamines in the reaction with L-CbzValine*.

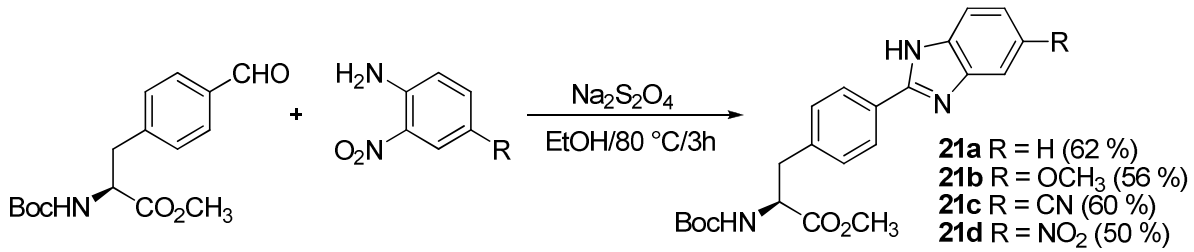
Reddy et al. adopted similar strategy for the synthesis of pyrrolidine-benzimidazole derivatives **19a**–**c** and **20a**–**c** (*Scheme 9*).[24] The activation of the carboxylic acid of L-BnProline has however been accomplished by ethylchloroformate *via* mixed anhydride. Subsequent treatment with *o*-phenylenediamine and cyclization in acetic acid afforded Bn-protected derivatives **19a**–**c** in the yields of 83-88 %. Bn-group removal has been achieved by hydrogenolysis. This methodology provides an easy and convenient access to pyrrolidine-benzimidazole organocatalysts **20a**–**c** in good yields of 75-84 %. The catalytic scope of these derivatives was evaluated in direct asymmetric aldol and Michael addition reactions (*Scheme 23* and *25*).



Scheme 9. *Synthesis of pyrrolidine-benzimidazoles.*

4.3 Method III

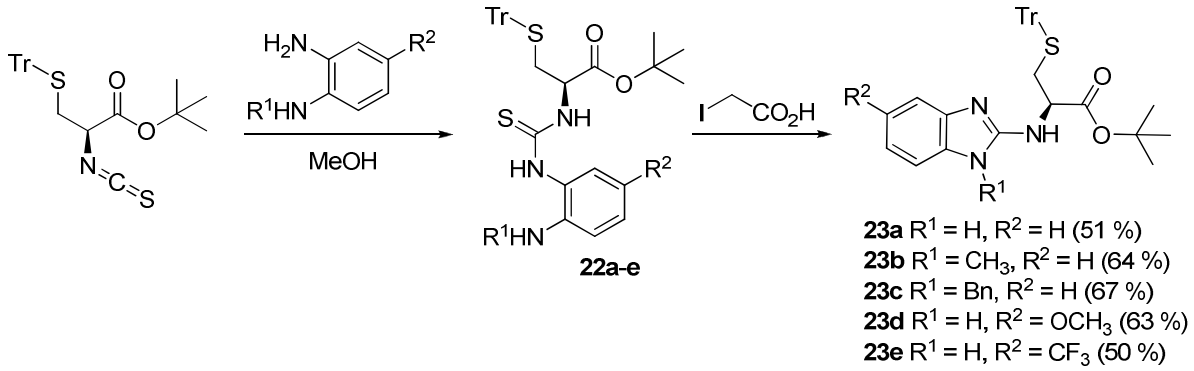
Batista *et al*. reported on novel optical chemosensors **21a**–**d** for anions and cations based on unnatural phenylalanine derivatives bearing benzo[*d*]imidazole as coordinating/reporting unit (*Scheme 10*).[25] The reaction has been carried out by the condensation of phenylalanine aldehyde with 4-substituted-2-nitroanilines under reductive condition of $Na_2S_2O_4$. Subsequent evaluation of the sensing properties of **21a**–**d** has been carried out in acetonitrile.



Scheme 10. *Synthesis of benzimidazolyl phenylalanine derivatives.*

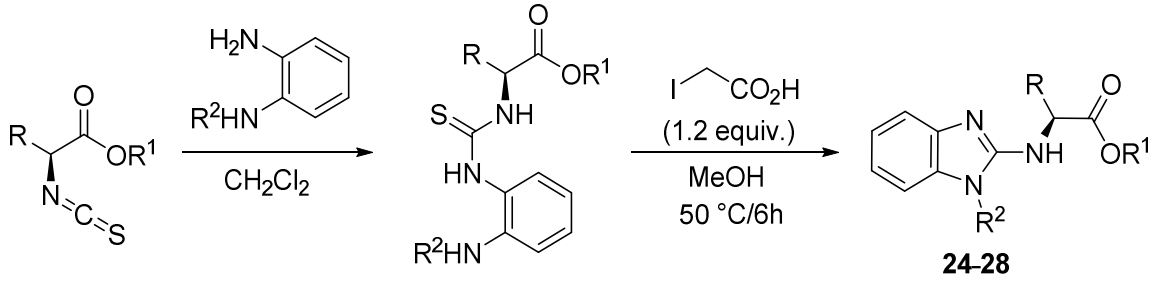
4.4 Method IV

Krasikovs *et al.* showed an interesting reaction of *S*-trityl *t*Bu-ester of L-cysteine bearing amino group converted into an isothiocyanate function. This class of amino acid derivatives undergo facile reaction with arene-1,2-diamines to afford thioureas **22a**–**e**. Such derivatives can be cyclized and desulfurized using iodoacetic acid (*Scheme 11*).[26] In this way, Krasikovs *et al.* have synthesized a series of L-cysteine derived benzo[*d*]imidazoles **23a**–**e** in the yields of 50-67 % having retained carboxylic function and attached various substituents R^1 and R^2.



Scheme 11. *Synthesis of L-cystine-derived benzo[d]imidazoles.*

This methodology has further been applied also to other α-amino acid esters such as L-phenylglycine, L-phenylalanine, protected L-serine/L-lysine and L-glutamic acid. These α-amino acids were readily converted into the corresponding benzo[*d*]imidazol-2-yl derivatives **24**–**28** in good to excellent yields. Each derivative has been synthesized in two series **a** and **b** with/without *N*-methyl group or hydrogen. Moreover, the conversion of the aforementioned α-amino acids into **24–28** was performed in a sequential manner without isolation and purification of the intermediate isothiocyanates and thioureas (*Scheme 12*).[26]



Scheme 12. *Synthesis of 2-aminobenzo[d]imidazoles **24-28**.*

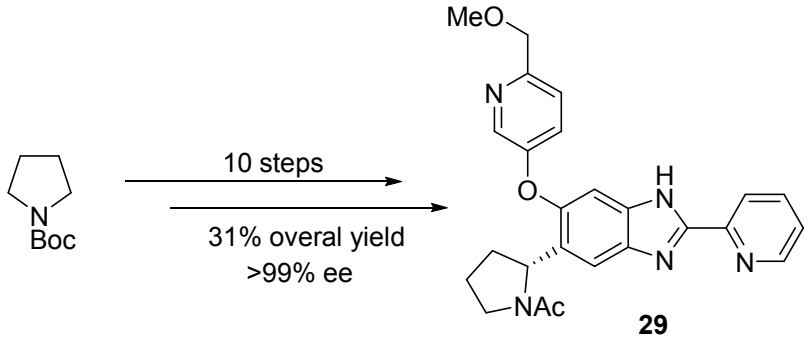
Table 1. Structure and yields of 2-aminobenzo[*d*]imidazoles **24**–**28**.

Product	Starting α-amino acid	R	R^1	R^2	Yield [%]
24a	Phenylglycine	Ph	CH_3	H	58
24b	Phenylglycine	Ph	CH_3	CH_3	75
25a	Phenylalanine	Bn	*t*Bu	H	84
25b	Phenylalanine	Bn	*t*Bu	CH_3	82
26a	Serine	$BnOCH_2$	CH_3	H	74
26b	Serine	$BnOCH_2$	CH_3	CH_3	91
27a	Lysine	$CbzNH(CH_2)_4$	CH_3	H	85
27b	Lysine	$CbzNH(CH_2)_4$	CH_3	CH_3	80
28a	Glutamic acid	$CH_3OOC(CH_2)_2$	CH_3	H	63

28b	Glutamic acid	$CH_3OOC(CH_2)_2$	CH_3	CH_3	59

4.5 Method V

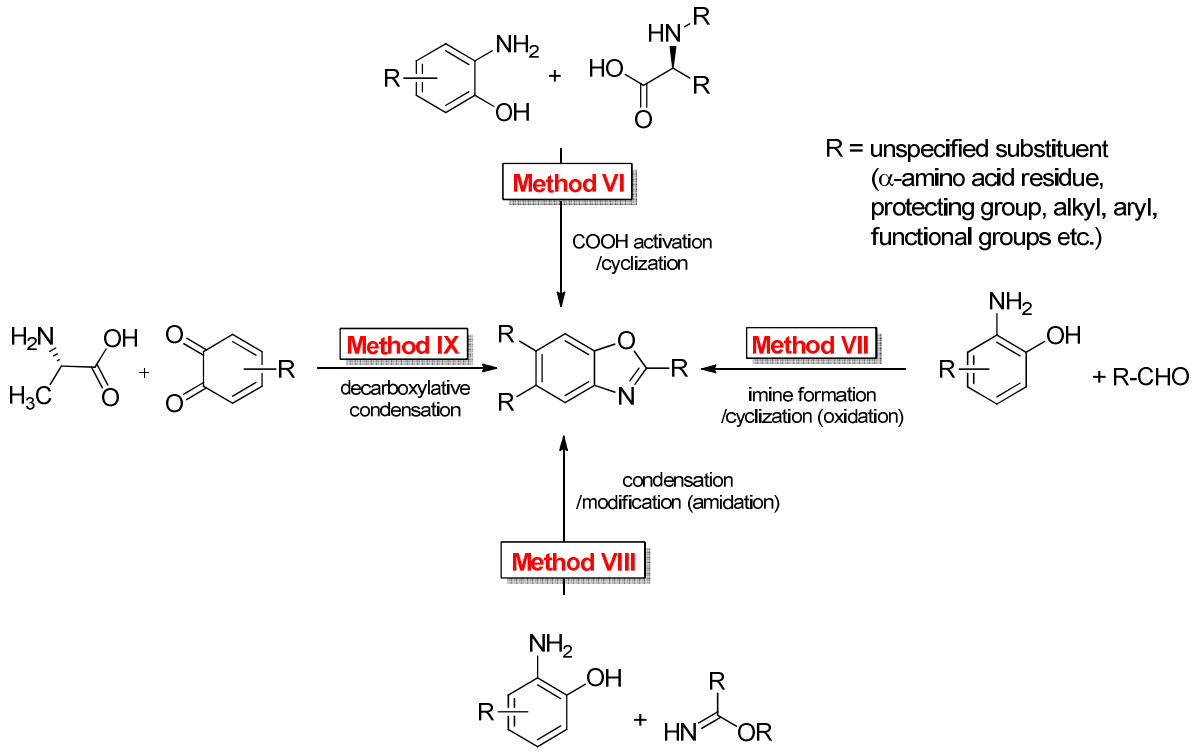
All the aforementioned Methods I-IV deal with the synthesis of benzo[*d*]imidazole-2-yl derivatives (C2-substituted). Klapars *et al.* showed an efficient and practical synthesis of glucokinase activator which, although not starting directly from an α-amino acid, led to benzo[*d*]imidazole **29** substituted with proline residue at C5 (*Scheme 13*).[27] The reaction sequence involves stereoselective lithiation of *N*-Boc-pyrrolidine, transmetallation to $ZnCl_2$, Negishi cross-coupling, amidation with α-picolinic acid, Boc to Ac protecting group exchange, nitration, S_NAr reaction, nitro group reduction to 1,2-diamine and subsequent cyclization using H_3PO_4. Target molecule **29** was isolated in 31% overall yield and more than 99% optical purity.



Scheme 13. *Synthesis of glucokinase activator based on benzo[d]imidazole.*

5. Synthetics approaches leading to benzo[*d*]oxazoles

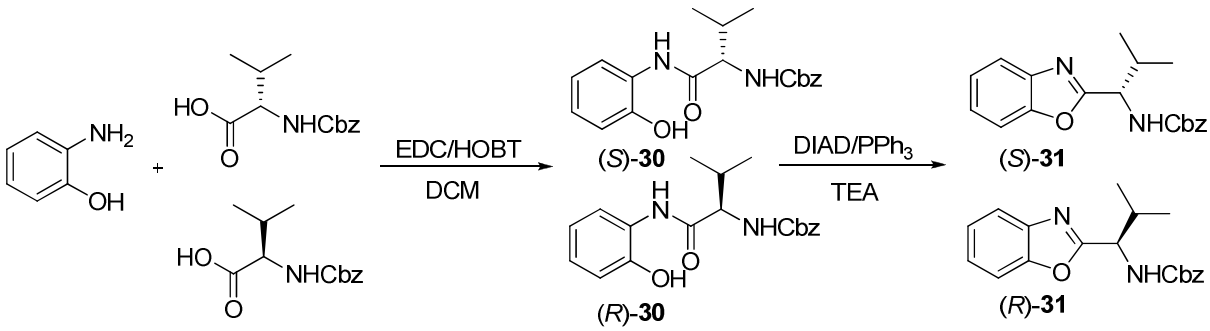
Similarly as for the aforementioned benzo[*d*]imidazole derivatives, the most expected are C2-substituted benzo[*d*]oxazoles. The precursors and reaction types are very similar to benzo[*d*]imidazoles and are summarized in *Scheme 14*. Again we can divide the available procedures in methods VI–IX that will be discussed in the subsequent chapters in more details.



Scheme 14. *The general synthetic approaches to benzo[d]oxazoles bearing α-amino acid residue.*

5.1 Method VI

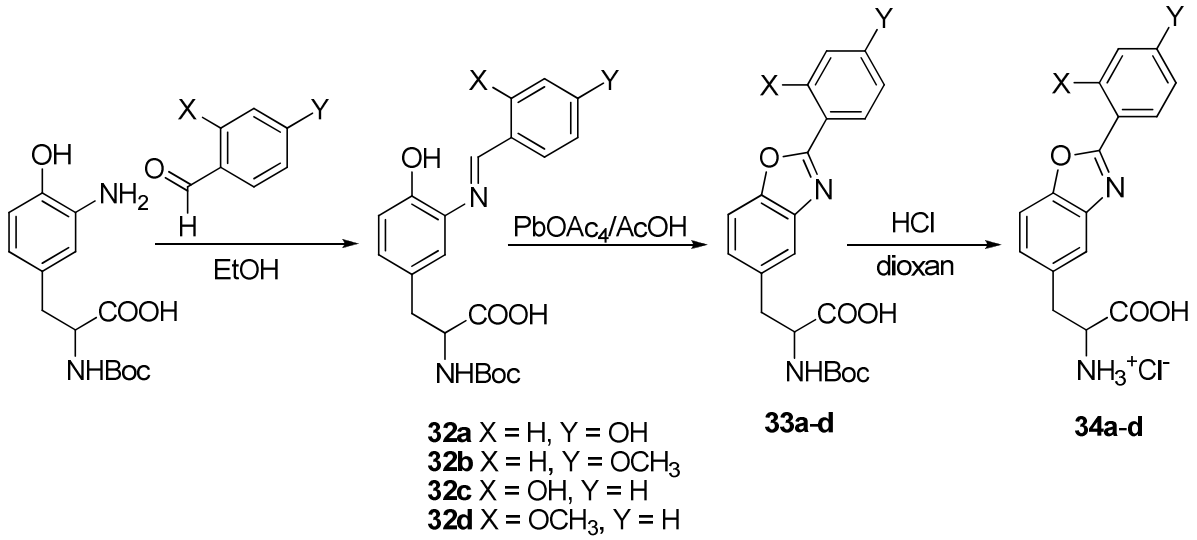
Similarly to *o*-phenylenediamine for benzo[*d*]imidazoles, 2-aminophenol represents the most widely employed synthetic precursor for benzo[*d*]oxazoles. This compound can be amidated *via* activated carboxylic acid of an α-amino acid and subsequently cyclized by intramolecular Mitsunobu reaction as shown by Hou *et al.* (*Scheme 15*).[28] Both Cbzvaline enantiomers (*R*)-**30** and (*S*)-**30** were applied in the reaction sequence affording compounds (*R*)-**31** and (*S*)-**31** in very low yields. In addition, the Cbz protecting group can be removed by hydrogenolysis using H_2/Pd/C system and the free amino group converted to azido function.



Scheme 15. *Synthesis of chiral benzo[d]oxazol-2-yl derivative* ***31****.*

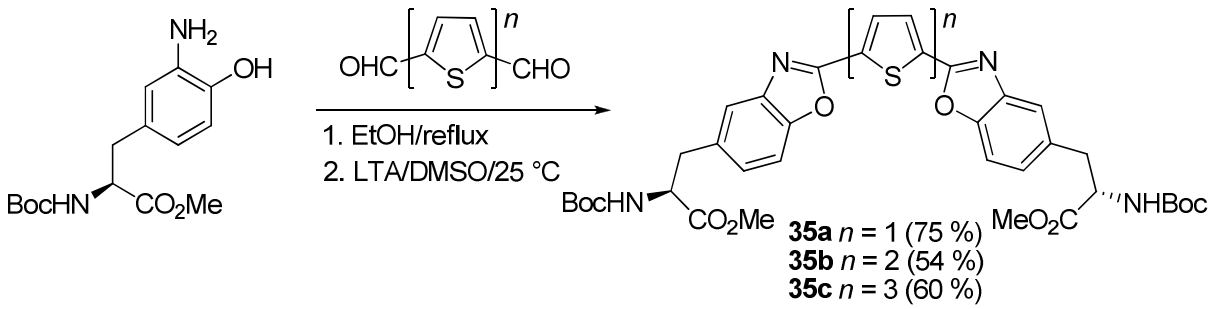
5.2 Method VII

4-Substituted 2-aminophenole, prepared by the reduction of corresponding nitro compound, was also used as starting materials by Rzeska *et al.* (*Scheme 16*).[29] The 4-substituent represents alanine residue (no stereochemistry given). The reaction sequence involves formation of a Schiff base by the reaction with substituted benzaldehydes and subsequent cyclization of the hydroxy imines **32a**–**d** to benzo[*d*]oxazole derivatives **33a**–**d** in the presence of lead tetracetate. Final acid-catalyzed Boc group removal afforded compounds **34a**–**d** (Box-Ala) substituted at positions 2'and 4' which were isolated as salts. The total yield of the reaction sequence was only about 10 %.



Scheme 16. *Synthesis of alanine residue containing phenyl-benzo[d]oxazoles* ***34a-d****.*

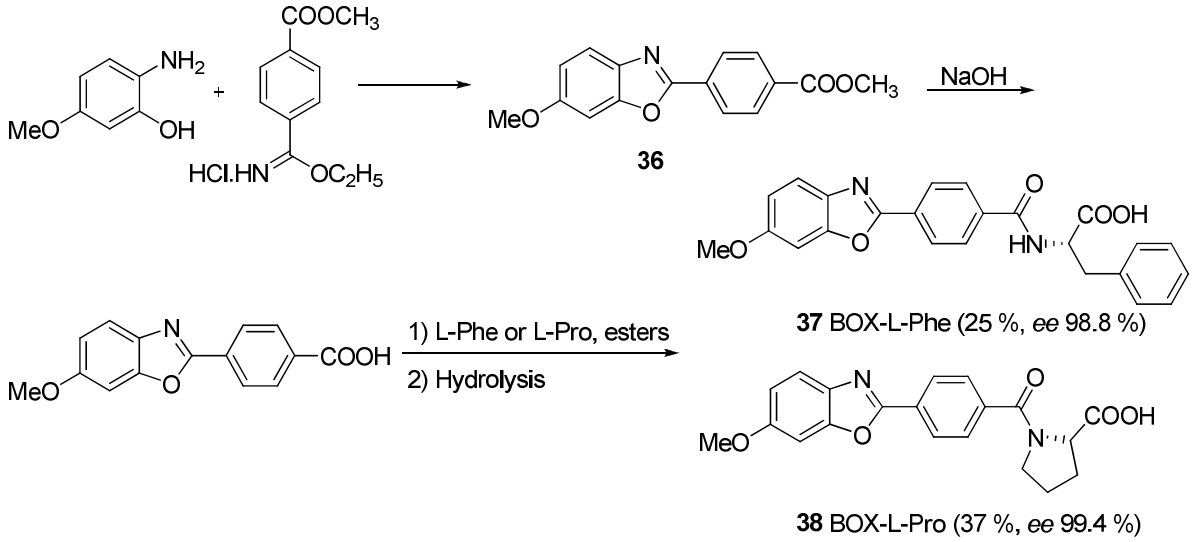
Costa *et al.* have used similar, 4-substituted 2-aminophenole precursor for twofold condensation with (oligo)thiophene-2,5-dicarbaldehydes (*Scheme 17*).[30] Chromophores **35a**–**c** bearing heteroaromatic π-conjugated thienylene bridge and benzoxazole units were synthesized in moderate to good yields and their photophysical properties were further evaluated. These heteroaromatic bisamino acid derivatives were applied as fluorescent markers and probes for FRET studies in peptides.



Scheme 17. Synthesis of fluorescent bis-alanine benzo[d]oxazole derivatives 35.

5.3 Method VIII

2-Aminophenole can also be condensed with imidoesters as shown by Kondo *et al.* (*Scheme 18*).[31] 5-Methoxy-2-aminophenol was treated with ethyl-4-methoxycarbonylbenziimidoester hydrochloride to afford benzo[*d*]oxazole **36** which, upon hydrolysis of the ester function, was peripherally modified with L-phenylalanine and L-proline esters to afford compounds **37** (BOX-L-Phe) and **38** (BOX-L-Pro). It turned out that these newly synthesized derivatives are of great use as chiral HPLC stationary phase capable to separate various optically active amines.

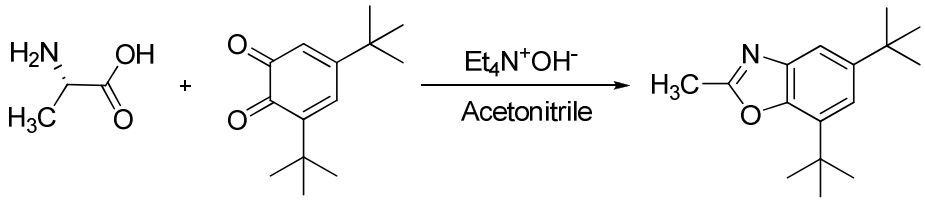


Scheme 18. *Synthesis of chiral HPLC stationary phases BOX-L-Phe and BOX-L-Pro.*

5.4 Method IX

Zwan *et al.* have shown that the reaction of an α-amino acids with *o*-benzoquinones is unique in the fact that the expected Strecker degradation does not occur. Instead of this, a decarboxylative condensation reaction between L-alanine and 3,5-di*tetrt*butylbenzoquinone takes place affording benzo[*d*]oxazole **39** (*Scheme 19*).[32] The new reaction appears to be general for other α-amino acids and specific for quinones. However, it should be noted that,

although starting from α-amino acid, this reaction does not afford benzo[*d*]oxazole derivatives bearing an α-amino acid residue in terms of preserving the stereogenic center.



39 (80 %)

Scheme 19. *Decarboxylative condensation of α-amino acids with benzoquinone.*

6. Modern applications of benzo[*d*]imidazoles and benzo[*d*]oxazoles

It should be noted that benzo[*d*]imidazole and benzo[*d*]oxazole derivatives bearing an α-amino acid residue and their prospective applications represent currently not well explored research area. Few examples of their applications ranging from the asymmetric synthesis (ligands or organocatalysts) to biological uses can be found in the current literature. Hence, in the subsequent chapter will be discussed such applications.

6.1 Asymmetric synthesis

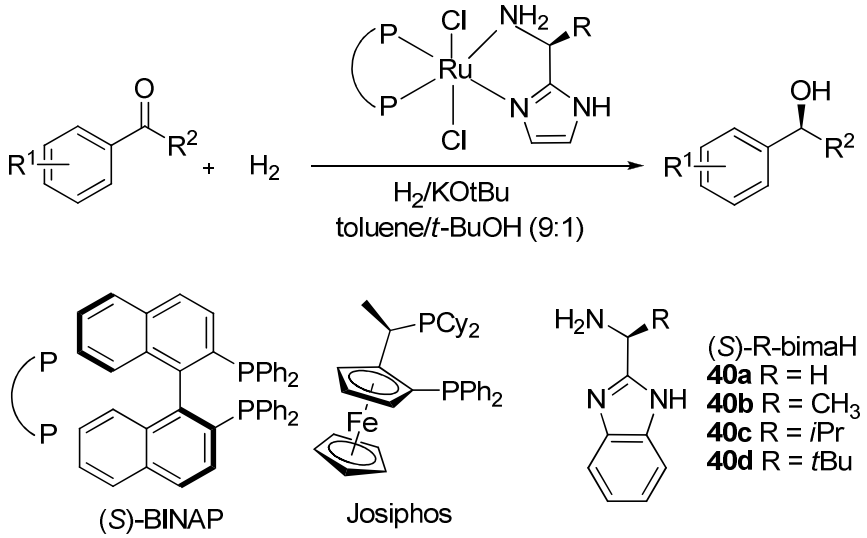
Optically active (pure) compounds bearing either chelating or reactive sites, and their prospective applications in asymmetric synthesis/catalysis represent tempting and challenging area of organic chemistry. Beside many well-established (privileged) ligands,[33] development of new catalysts, ligands and reagents with modified structure and enhanced catalytic activity is currently attracting huge research attention. In asymmetric reactions, the optically active organic derivatives may play usually two roles:

- optically active auxiliary chelating a (transition) metal - ***ligand***,
- optically active ***organocatalyst***.

6.1.1 Ligands

Li *et al*. reported on bidentate aminomethyl-substituted benzo[*d*]imidazole ligand **40a** coordinating, jointly with a bidentate phosphine, ruthenium(II)dichloride. This complex was able to catalyze hydrogenation of aryl ketones (*Scheme 20*).[34] Introduction of an asymmetric center at the benzylidene moiety of **40a** renders optically active ligands **40b–d** [(*S*)-R-bimaH],

which allowed to perform asymmetric hydrogenation of the parent acetophenone to (*S*)-1-phenylethanol with *ee* up to 91 % (*Table 2*, entries 1–4). When going from achiral **40a** to chiral **40b**–**d** we can see improvement of the achieved enantioselectivity by 10 to 14 %. Hence, easily obtained alanine-derived ligand **40b** was used for the reduction of several other ketones (*Table 2*, entries 5–12). Variously substituted acetophenones (electron donors/acceptors), benzophenone and 2-acetylthiophene were smoothly converted to the corresponding (*S*)-alcohols. Surprisingly, reduction of unsymmetrical benzophenone led to the alcohol with opposite absolute configuration (*Table 2*, entry 10). Anyway, with benzo[*d*]imidazole ligands, the asymmetric hydrogenation can be carried out on a large number of ketones with the chemical and optical yields up to 99 % and S/C ratio up to 50.000. In contrast to common hydrogenations carried out in alcohols, the benzo[*d*]imidazole residue allowed for hydrogenation to be uncharacteristically conducted in nonprotic solvents (toluene).



Scheme 20. *Asymmetric hydrogenation of aryl ketone catalyzed by P,P-Ru-(S)-R-bimahcomplexes.*

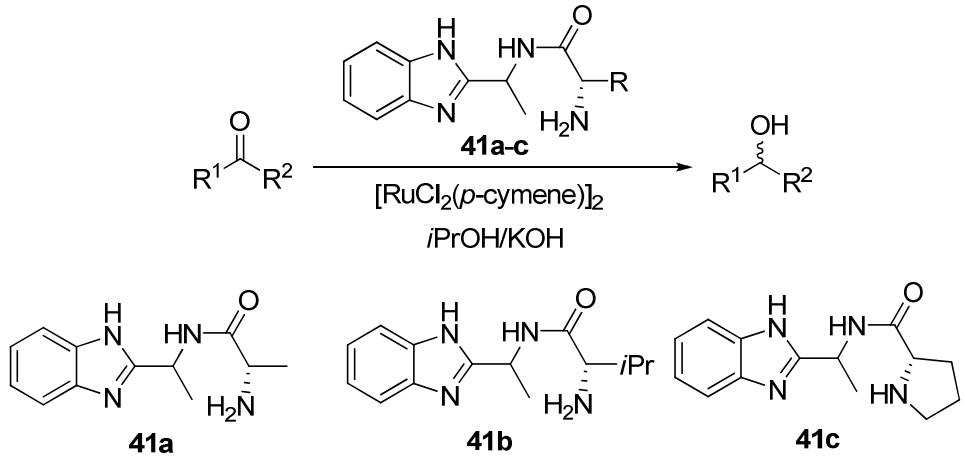
Table 2. Asymmetric hydrogenation of prochiral ketones by Ru-complexes of **40a–d**.

Entry	Ketone R^1/R^2	Catalyst composition	Time [h]	Yield [%]	*ee* [%] (configuration)
1	H/CH_3	**40a**/(*S*)-BINAP	8	>99	77 (*S*)
2	H/CH_3	**40b**/(*S*)-BINAP	8	>99	91 (*S*)
3	H/CH_3	**40c**/(*S*)-BINAP	12	>99	87 (*S*)
4	H/CH_3	**40d**/(*S*)-BINAP	10	>99	91 (*S*)
5	H/CH_3	**40b**/Josiphos	2	>99	96 (*S*)

6	4-OCH_3/CH_3	**40b**/Josiphos	16	95	97 (*S*)
7	4-CF3/CH_3	**40b**/Josiphos	8	90	82 (*S*)
8	2-CH_3/CH_3	**40b**/Josiphos	8	>99	95 (*S*)
9	3-Br/CH_3	**40b**/Josiphos	6	>99	92 (*S*)
10	2-Cl/Ph	**40b**/Josiphos	24	95	99 (*R*)
11	Th[a]/CH_3	**40b**/Josiphos	12	92	94 (*S*)
12	H/CH_2CH_3	**40b**/Josiphos	12	>99	97 (*S*)

[a]Thiophene-2-yl instead of R^1Ph moiety.

Based on alanine-derived benzo[*d*]imidazole **40b**, Li *et al.* prepared a series of extended molecules **41a**–**c** (*Scheme 21*).[35] Catalytic activity of the *in situ* generated complexes with[$RuCl_2$(*p*-cymene)] dimer were subsequently evaluated in asymmetric transfer hydrogenation (ATH) of prochiral ketones using *i*PrOH/KOH system (*Table 3*). Alanine and valine derived ligands **41a** and **41b** showed low catalytic activity with achieved *ee* not exceeding 12 %, which was assigned to the presence of free NH_2 group.



Scheme 21. *Asymmetric transfer hydrogenation reaction.*

Table 3. Asymmetric hydrogenation transfer using **41c**/[$RuCl_2$(*p*-cymene)]$_2$ system.

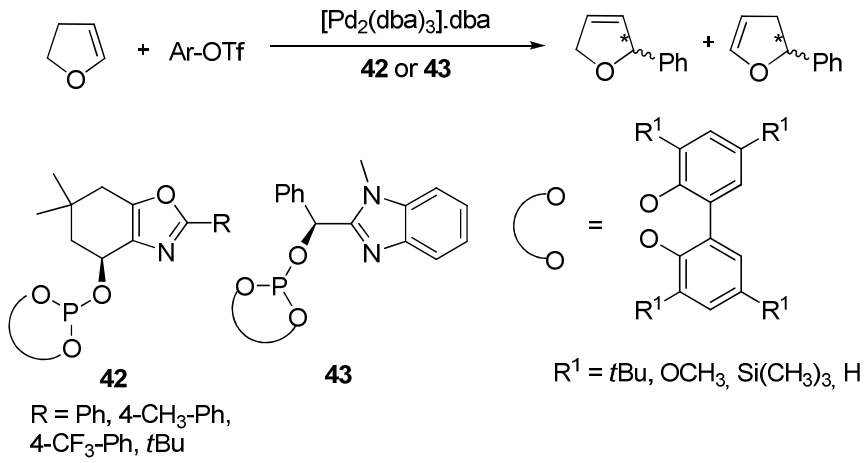
Entry	Ketone R^1/R^2	Temperature [°C]	Time [h]	Conversion [%]	*ee* [%] (configuration)
1	Ph/CH_3	25	5	12	11 (*R*)
2	Ph/CH_3	40	3	29	10 (*R*)
3	Ph/CH_3	60	2	59	12 (*R*)
4	Ph/CH_3	110	0.25	57	61 (*R*)
5	Ph/CH_3	140	0.25	70	64 (*R*)
6	3-OCH_3Ph/CH_3	140	0.25	6880[a]	55 (*R*)
7	4-OCH_3Ph/CH_3	140	0.25	3120[a]	55 (*R*)

8	2-ClPh/CH_3	140	0.25	1440[a]	15 (*R*)
9	Ph/-$CH_2CH_2CH_2$-	140	0.25	240[a]	-
10	Ph/Pr	140	0.25	800[a]	43 (*S*)
11	Naft-1-yl/CH_3	140	0.25	320[a]	43 (*S*)
12	CH_3/CH_2CH_3	140	0.25	560[a]	-

[a]Turnover frequency in h^{-1} (TOF) at S/C 2000:1.

Cyclic proline derivative **41c** showed similar low enantioselectivity of 11 % *ee* at 25 °C (*Table 3*, entry 1). However, the catalytic activity of this Ru-complex showed reversed temperature effect (*Table 3*, entries 2–5). Increasing the temperature up to 140 °C resulted in quick reaction time (0.25 h), conversion up to 70 % and enantiomeric excess of 64 %. Hence, the substrate scope has been examined at standard conditions (140 °C, 15 min, S/C 2000:1) with prochiral ketones of various structures (*Table 3*, entries 6–12). As can be seen, this catalytic system failed to enantioselectively reduce cyclic and aliphatic ketones such as 3,4-dihydronaphthalen-1-one (*Table 3*, entry 9) and butan-2-one (*Table 3*, entry 12). Comparing with the previous ligands **40**, the extended molecules **41** showed lower catalytic performance in ATH reaction.

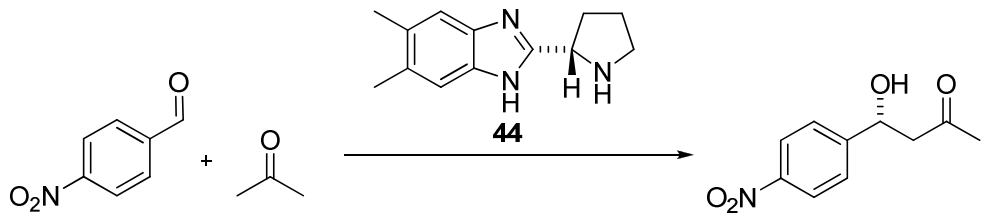
Phosphite-oxazoles/benzo[*d*]imidazoles **42** and **43**, with a pattern similar to studied α-amino acid derivatives, were synthesized and further studied by Mazuela *et al*. (*Scheme 22*).[36] Catalytic activity of these ligands coordinating Pd(0) were examined in thermal and microwave-assisted asymmetric intermolecular Heck reaction between 2,3-dihydrofuran and various triflates (Ar-OTf). With the benzo[*d*]imidazole ligand **43** in particular, the achieved conversions were within the range of 7-24 % with *ee* up to 75 %. Under microwave-irradiation, the conversion was significantly improved to 69 % (85:15), the reaction time dropped to 30 min (from 24 h) and the achieved *ee* was 76 %.



Scheme 22. *Asymmetric Heck reaction.*

6.1.2. Organocatalyst

Vincent *et al*. showed very nice example of application of 5,6-dimethylbenzo[*d*]imidazole linked to L-proline residue in asymmetric aldol reaction (*Scheme 23*).[37] A new chiral benzimidazole-pyrrolidine **44** (BIP) was able to organocatalyze aldol process between the acetone and 4-nitrobenzaldehyde in the presence of an Brönsted acid. In this work, type and amount of the acid used, various solvents and organocatalyst loads were screened (*Table 4*). The initial reaction carried out without an acid provided the aldol in 40% yield and 44% *ee* (*Table 4*, entry 1). From the acetic acid-catalyzed reactions carried out in various solvents (*Table 4*, entries 2–6) we can conclude that the reaction in THF provided the best trade-off between the achieved yield and enantiomeric excesses (70 and 64 %, respectively). However, when switching to trifluoroacetic acid (TFA), the conversions as well as the attained *ee*'s were improved significantly (*Table 4*, entries 7–11). The reaction provides reasonable amount and optical purity of target aldol even when the catalyst/acid loads drop to 2 mol. % or when using THF solvent and only 1.1 eq. of the acetone. Interestingly, the reaction can also be organocatalyzed by **44** in a combination with trifluoromethanesulfonic acid as well as Lewis acid such as zinc(II)triflate (Table 4, entries 12–13).



Scheme 23. *Benzimidazole-pyrrolidine (BIP) as chiral organocatalysts for aldol process.*

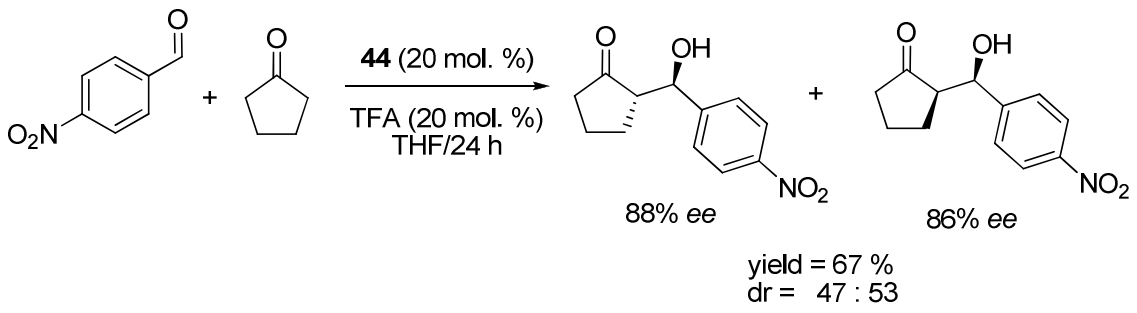
Table 4. Condition screening for aldol process shown at *Scheme 23*.

Entry	Catalyst **44** [mol. %]	Acid [mol. %]	Temperature [°C]	Solvent	Time [h]	Yield [%]	*ee* [%][c]
1	30	-	20	DMSO[a]	8	40	44
2	20	AcOH (20)	–20	DMSO[a]	4	65	54
3	20	AcOH (20)	–20	DMF[a]	24	61	75
4	20	AcOH (20)	–20	THF[a]	8	70	64
5	20	AcOH (20)	–20	DCM[a]	18	92	36
6	20	AcOH (20)	–20	Acetone[a]	4	78	62
7	20	TFA (20)	–20	Acetone	18	86	82

8	10	TFA (10)	–20	Acetone	24	95	80
9	2	TFA (2)	–5	Acetone	24	87	82
10	20	TFA (20)	–5	THF[b]	24	67	82
11	5	TFA (5)	–5	THF[b]	48	69	80
12	20	TfOH (20)	–20	Acetone	24	84	80
13	20	$Zn(OTf)_2$ (20)	20	Acetone	17	87	74

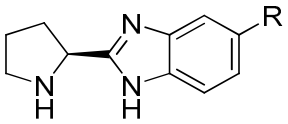
[a]Acetone 25 eq.; [b]Acetone 1.1 eq.; [c]All aldols possess (*R*)-configuration.

In addition to the aldol process carried out with acetone (*Scheme 23*), the catalytic activity of **44** has also been tested in a reaction with cyclopentanone (*Scheme 24*). Performing the reaction in THF with 1.1 eq. of cyclopentanone and catalyzed by 20 mol. % of **44** and TFA, a mixture of two diastereoisomers was obtained in 67% yield with 88% and 86% *ee* for *anti*- and *syn*-diastereoisomers, respectively.



Scheme 24. *BIP-organocatalyzed aldol process utilizing cyclopentanone.*

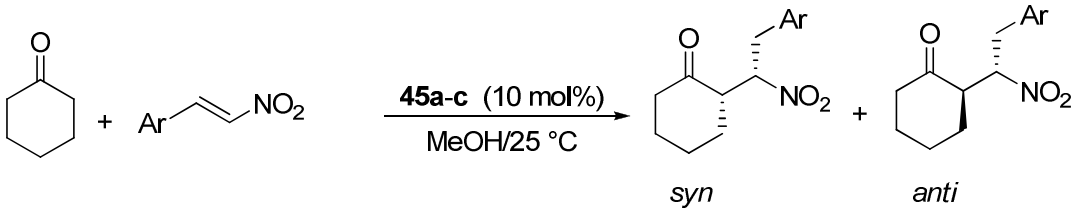
Three years later after Vincent *et al*. paper, Reddy *et al*. extended family of BIP organocatalysts by compounds **45a**–**c** (*Figure 11*).[24] Whereas the original synthesis of **44** has been accomplished by Method I, Reddy has utilized more convenient Method II (see above). Organocatalysts **45a**–**c** were further applied in aldol process similar to that shown in *Scheme 23* (15% mol. catalysis, NMP/DMSO/DMF/MeOH/acetone solvents, reaction time of 1–10 h) achieving the yields and enantiomeric excesses within the range of 60–93 and 8–54 %, respectively. Substrate scope screening carried out on various aromatic aldehydes furnished yields and *ee*'s within the range of 65–93 and 27–49 %, respectively.



45a R = H
45b R = CH_3
45a R = $COOCH_3$

Figure 11. *Further modification of BIP organocatalyst.*

BIP organocatalysts **45a**–**c** were further utilized also in Michael additions between cyclohexanone and various (hetero)aryl-substituted nitroolefins as shown in *Scheme 25*.[24] Although all three catalyst provided the product in reasonable chemical yields of 85–95 %, noticeable asymmetric induction with *ee* of 49 % was observed only with parent BIP catalyst **45a** (*Table 5*, entries 1–3). Hence, further additions were organocatalyzed by derivative **45a** delivering the chemical yields of 82–95 % and low enantioselectivities with *ee*'s of 11–37 %.



Scheme 25. *Michael addition of cyclohexanone to nitrostyrenes organocatalyzed by BIP.*

Table 5. Results of Michael addition reactions organocatalyzed by BIP derivatives **45a**–**c**.

Entry	Olefin R	Catalyst	Time [h]	Yield [%]	*Syn*/*anti*	*ee* [%][c]
1	Ph	**45a**	2	95	99/1	49
2	Ph	**45b**	2	85	-[a]	27
3	Ph	**45c**	2	87	-[a]	15
4	2-CH_3OPh	**45a**	6	95	98/2	30
5	4-CH_3OPh	**45a**	7	92	99/1	11
6	Furan-2-yl	**45a**	6	85	99/3	37
7	Thiophen-2-yl	**45a**	6	82	96/4	23

[a]Not given.

Almaşi *et al*. have studied molecules **46a**–**d** bearing similar, although not α-amino acid-derived, pattern as previous BIP chiral organocatalysts **44** and **45** (*Figure 12*).[38]

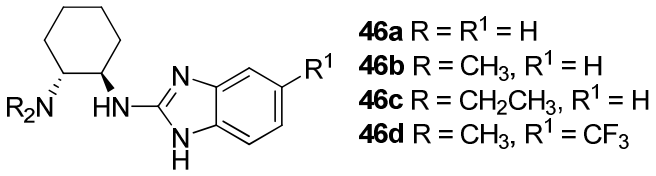
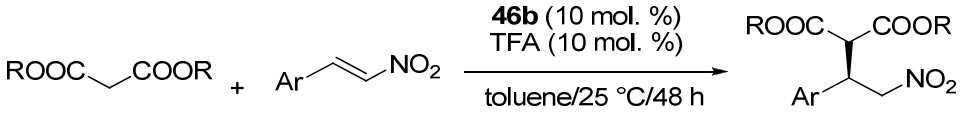


Figure 12. *Structure of BIP-related trans-cyclohexanediamine-benzo[d]imidazoles* ***46a-d****.*

They demonstrated that *trans*-cyclohexanediamine-benzo[*d*]imidazoles **46a**–**d** promote conjugate addition of diethylmalonate to nitroalkenes with excellent yields and very good enantioselectivities (*Scheme 26*). Initial screening showed that organocatalyst **46b** provided the best performance among all studied compounds **46a**–**d**. The best reaction conditions were set to: toluene, 25 °C and 10 mol. % of the catalyst **46b** and TFA as co-catalyst, respectively (*Table 6*). As can be seen from this data, increasing the bulkiness of the malonate substituents significantly lowered the attained chemical yields. Anyway, with diethyl malonate as a nucleophile, various aromatic and heteroaromatic nitroolefins undergo smooth reaction achieving almost quantitative isolated yields (flash chromatography) and enantiomeric excesses ranging from 88 to 94 %.



Scheme 26. *Organocatalyzed conjugated addition of dialkylmalonates with nitroalkenes.*

Table 6. Structures, yields and enantiomeric excesses achieved for addition of dialkylmalonates to nitroalkenes.

Entry	Malonate R	Nitroalkene Ar	Yield [%]	*ee* [%]
1	Et	Ph	97	92
2	Me	Ph	95	89
3	*i*Pr	Ph	42	89
4	*t*Bu	Ph	< 5	Nd
5	Et	4-ClPh	95	88
6	Et	2-CF_3Ph	97	90
7	Et	2,4-diClPh	96	94
8	Et	4-CH_3Ph	98	88
9	Et	4-CH_3OPh	98	88
10	Et	Thiophen-2-yl	98	87

In addition to malonates, a wide variety of 1,3-dicarbonyl compounds bearing active methylene groups such as diesters, ketoesters and diketones were further utilized in the reaction with nitroolefins organocatalyzed by **46b**. The Michael adducts were obtained in high yields (92–96 %) and enantioselectivities of 70–96 % *ee*.

7. Biological profile of benzo[*d*]imidazole and benzo[*d*]oxazole derivatives bearing an α-amino acid residue

There are few reports in the current literature on benzo[*d*]imidazole and benzo[*d*]oxazole derivatives bearing an α-amino acid residue that showed biological or pharmaceutical properties. In this chapter, a very brief survey of such applications will be given.

Aminabhavi *et al.* reported benzo[*d*]imidazoles **47a**–**c** (*Figure 13*) which were easily synthesized by Method I (see above). Upon complexation with dimethyldichlorosilane, they showed antibacterial and antiinflamatory activities.[39]

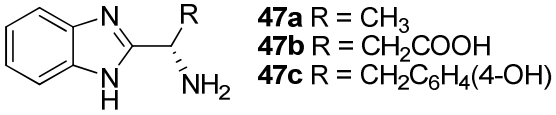
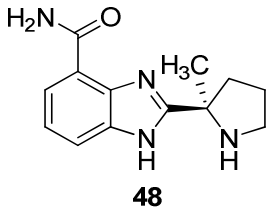


Figure 13. *Antibacterial and antiinflamatory active benzo[d]imidazoles **47**.*

Benzo[*d*]imidazole derivative **48** (*Figure 14*) bearing proline fragment was used as poly(ADP-ribose) polymerase (PARP) inhibitor.[40] PARP is a family of enzymes that cleaves nicotinamide adenine dinucleotide (NAD) to nicotinamide and ADP-ribose. Molecule **48**, named as ABT-888, showed nanomolar PARP-inhibition concentrations and has been shown to potentiate DNA damaging chemotherapy and radiation.



48

Figure 14. *Structure of ABT-888.*

Novel actinonin derivatives bearing substituted benzo[*d*]imidazole core **49** have been synthesized by Zhang *et al.* (*Figure 15*).[23] These derivatives were tested for their antibacterial

activities against various strains and the results were compared with the commercial Cefoperazone antibiotic.

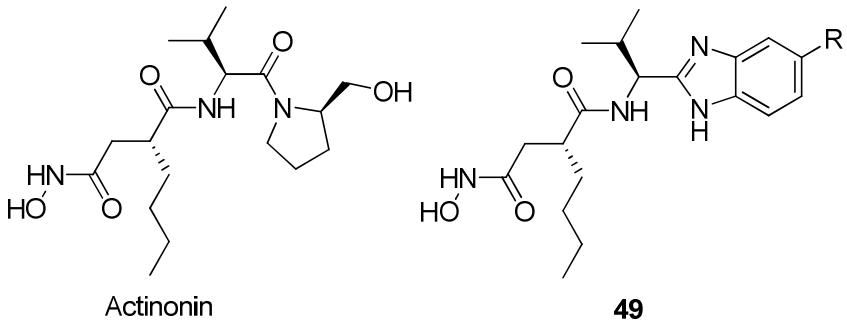


Figure 15. *Peptidomimetic modification of actinonin made by Zhang.*

Two isolobal benzo[*d*]oxazole and benzo[*d*]imidazole derivatives **50** and **51** (*Figure 16*) bearing hydroxyethyl substituent at C2 (similar to α-amino acid fragment) were synthesized and further investigated by Elnima *et al.*[41] Both derivatives were tested for their antibacterial and antifungal activity. Surprisingly, only benzo[*d*]oxazole derivative **50** showed such activities. The benzo[*d*]imidazole derivative **51** was devoid of any activity.

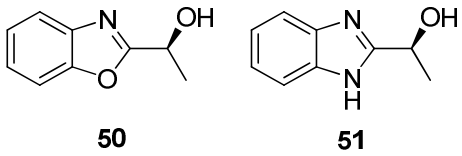


Figure 16. *Isolobal benzo[d]oxazole and benzo[d]imidazole derivatives (not) possessing antibacterial and antifungal activity.*

Starting from benzo[*d*]oxazole-2-thiol, Farhan *et al.* have shown the synthesis of derivatives **52a**–**c** (*Figure 17*).[42] The reaction sequence leading to these molecules involves *S*-alkylation of the starting material using ethyl bromoacetate, hydrolysis and activation of the ester/carboxylic acid functions and subsequent amidation using ethyl esters of glycine (**a**), L-tyrosin (**b**) and L-phenylalanine (**c**). These derivatives were further screened for antimicrobial (antibacterial and antifungal) activities.

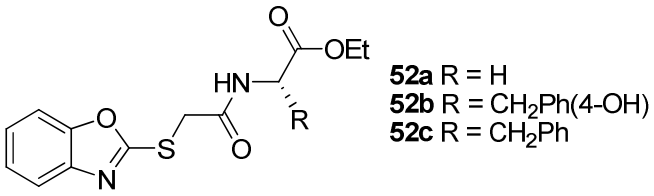


Figure 17. *Benzo[d]oxazole derivatives exhibiting antibacterial and antifungal activities.*

HDAC (histone deacetylase) inhibitors **53a**–**h** bearing benzo[*d*]oxazole cap moiety were developed by Hou *et al.* (*Figure 18*).[28] These molecules possess the α-amino acid residue bridged *via* triazine ring and extended by hydroxylamide function (Zn-binding function). The synthesis involves three-component click reaction (2-aminophenole, α-amino acid derived triazines and an alkyne). In the first stage of the research, only racemic mixtures of **53a**–**h** were screened, which revealed the valine derivative **53c** as the most promising lead compound. Moreover, the (*S*)-enantiomer showed higher inhibition activity (IC_{50} = 7 nM) than (*R*)-enantiomer (IC_{50} = 31 nM).

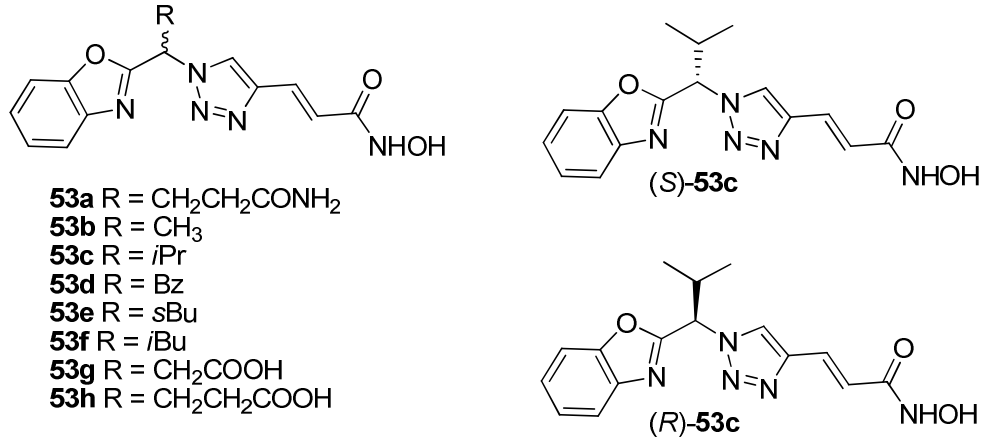


Figure 18. *Novel HDAC inhibitors based on benzo[d]imidazole.*

8. Perspectives of α-amino acid derived benzo[*d*]imidazoles and benzo[*d*]oxazoles

The literature search performed above revealed that benzo[*d*]imidazole and benzo[*d*]oxazole derivatives represent undoubtedly an interesting class of heterocyclic compounds. A fusion of the aromatic benzene with heteroaromatic imidazole or oxazole renders target molecules that possess plenty of interesting properties such as for instance tautomerism (benzo[*d*]imidazole), acid-base character, equivocal reactivity (both with electrophiles and nucleophiles/bases) and facile synthetic access. Well-known natural/synthetic molecules bearing benzo[*d*]imidazole or benzo[*d*]oxazole scaffold are alpha-ribazole (Vitamine B_{12}) or Flunoxaprofen and Zoxazolamine drugs. Another great area of benzo[*d*]imidazole applications are nitrogen heterocyclic carbenes (NHCs). Anyway, this work focuses on benzo[*d*]imidazole and benzo[*d*]oxazoles bearing an α-amino acid residue. In principal, the amino acid residue can be attached at all available positions around the heterocycle. However, this literature search showed that derivatives bearing an α-amino acid

residue attached at C2 appearing most often. The most widely employed precursors for the synthesis of target benzo[*d*]imidazole or benzo[*d*]oxazole derivatives are benzene-1,2-diamine and 2-hydroxybenzeneamine (*o*-phenylenediamine and 2-hydroxyaniline), which may be condensed with acids, esters, mixed anhydrides, imidoesters, aldehydes and diketones. Overall nine general synthetic methods have been revealed (Methods I-V and Methods VI-IX).

The most exciting are novel applications of benzo[*d*]imidazoles or benzo[*d*]oxazoles. In this respect, two major areas were found. The first one concerns asymmetric catalysis, while the second application is in pharmaceutical chemistry.

In the asymmetric catalysis, the benzo[*d*]imidazole and benzo[*d*]oxazole derivatives bearing an α-amino acid residue were applied either as ligands as well as organocatalysts. The most successful application of benzo[*d*]imidazole-derived ligand **40b** (*Scheme 20*) has been demonstrated by Li *et al*. The complex of **40b** with $RuCl_2$ and Josiphos (*Figure 19*) showed outstanding catalytic activity in hydrogenation of prochiral aryl ketones achieving chemical and optical yields of 99 % (*Scheme 20*, *Table 2*).

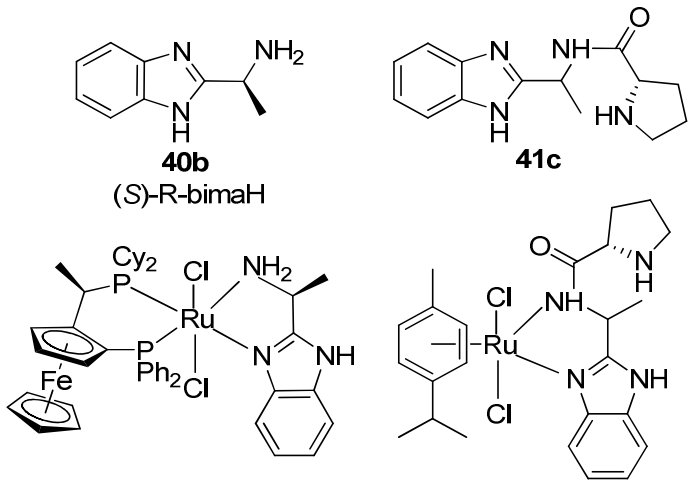
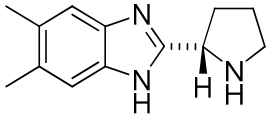


Figure 19. *Two benzo[d]imidazole ligands* ***40b*** *and* ***41c*** *and their envisaged Ru(II) complexes applied in reduction of prochiral ketones*

On the other hand, similar ATH reaction using exclusively nitrogen ligand **41c** coordinating Ru(II) precursor (*Figure 19*), showed much modest outcomes (up to 70% chemical and 64% optical yields) although bearing an additional proline residue. Hence, one could envisage crucial role of the phosphine ligand which is most likely responsible for the higher enantioselectivity achieved with **40b**.

The most successful application of benzo[*d*]imidazole and benzo[*d*]oxazole derivatives with amino acid chain has been shown in aldol reaction by Lacoste *et al*. (*Scheme 23*, *Table 4*). Benzo[*d*]imidazole **44** linked at the C2 to proline residue (*Figure 20*) organocatalyzed, jointly

with various Brönsted acids, the reaction between 4-nitrobenzaldehyde and acetone with 92% chemical and 82% optical yields. Further modification of the parent BIP derivative did not lead to a better catalytic performance. This organocatalyst has also been applied in Michael type of reaction between nitrostyrenes and cyclohexanone (*Scheme 25*, *Table 5*). Whereas the resulting products were obtained in satisfactory chemical yields of 95 %, the enantiomeric excesses were only up to 49 %.



44

Figure 20. *The most successful organocatalyst – BIP.*

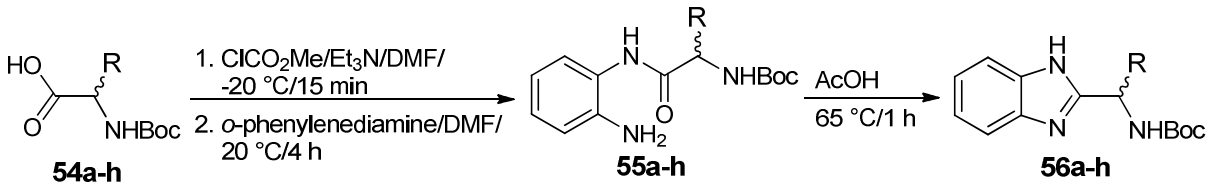
The biological applications of amino acid benzo[*d*]imidazole and benzo[*d*]oxazoles range from antibacterial, antifungal, anti-inflammatory activities to various inhibitors such as PARP or HDAC. Several most important examples with brief description of their action were demonstrated in *Figures 15–18*. Thus, beside the asymmetric catalysis, the molecules to which targets this doctoral thesis were also successfully applied in pharmacochemistry.

9. Experimental sections

9.1 Materials and instruments

The starting boc-protected α-amino acids **54a**–**h** are commercially available. The enantiomeric excesses were determined by high performance liquid chromatography (HPLC) with a Daicel Chiralcel OJ-H, Chiralcel OD-H, Chiralpak AS-H or Chiralpak AD-H columns using a mixture of isopropanol and the hexanes as the eluent. Evaporation and concentration *in vacuo* were performed at water aspirator pressure. Column chromatography (CC) was carried out with SiO_2 60 (particle size 0.040–0.063 mm, 230–400 mesh; Merck) and commercially available solvents. Thin-layer chromatography (TLC) was conducted on aluminium sheets coated with SiO_2 60 F_{254} obtained from Merck, with visualization by a UV lamp (254 or 360 nm). Melting points (mp) were measured on a Büchi B-540 melting-point apparatus in open capillaries and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 400/500 and 100/125 MHz, with Bruker AVANCE 400 and AVANCE 500 instruments at 25 °C. Chemical shifts are reported in ppm relative to the signal of Me_4Si. Apparent resonance multiplicities are described as s (singlet), br s (broad singlet), d (doublet), dd (doublet of doublet), dt (doublet of triplet), t (triplet), q (quartet), and m (multiplet). Residual solvent signals in the ^{1}H and ^{13}C NMR spectra were used as the internal reference ($CDCl_3$ - 7.25 and 77.23 ppm; DMSO-d_6 2.55 and 39.51 ppm). Coupling constant are given in Hertz. Optical rotation values were measured on a Perkin Elmer 341 instrument; concentration *c* is given in g/100 mL MeOH. IR spectra were recorded on a Thermo Nicolet iS50 FTIR (Thermo Fisher Scientific inc. Waltham) spectrometer. Elemental analyses were performed on a Thermo Flash 2000 CHNS experimental organic analyser. High resolution MALDI MS spectra were measured on a MALDI mass spectrometer LTQ orbitrap XL (Thermo Fisher Scientific, Bremen, Germany) equipped with nitrogen UV laser (337 nm, 60 Hz). The LTQ orbitrap instrument was operated in positive ion mode over a normal mass range (*m*/*z* 50 - 1500) with the following setting of tuning parameters: resolution 100,000 at *m*/*z* = 400, laser energy 17 mJ, number of laser shots 5, respectively. The used matrix was 2,5-dihydroxybenzoic acid (DHB). Mass spectra were averaged over the whole MS record (30 s) for all measured samples.

9.2 General procedure for the synthesis *N*-unsubstituted benzo[*d*]imidazole



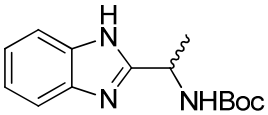
56a, R = Me (±) **56e,** R = *i*-Bu (*S*)
56b, R = Me (*R*) **56f,** R = *s*-Bu (*S*)
56c, R = Me (*S*) **56g,** R = CH_2Ph (*S*)
56d, R = *i*-Pr (*S*) **56h,** R = (1-Methylindol-3-yl)methyl (*S*)

Scheme 27. *Synthesis of benzo[d]imidazole linked with Boc protected α-amino acids.*

Methyl chloroformate (1.6 mL, 21.2 mmol) was added to a mixture of **54a**–**h** (21.2 mmol), triethylamine (3.0 mL, 21.2 mmol), and DMF (18 mL) at −20 °C. After 15 min of stirring, *o*-phenylenediamine (2.3 g, 21.2 mmol) was added and the reaction was stirred at 20 °C for 4 h. The solvent was evaporated *in vacuo* and the residue was portioned between water and EtOAc. The organic layer was washed with $NaHCO_3$ (5% aq.), brine, water, dried(Na_2SO_4) and the solvent was evaporated *in vacuo* to afford crude amino-amide **55a**–**h** (71–84 %), which was used directly in the cyclization.

A solution of compound **55a**–**h** (20.0 mmol) in glacial AcOH (10 mL) was heated at 65 °C for 1 h, the solvent was evaporated and the residue was portioned between water and EtOAc. The organic layer was washed with water, dried (Na_2SO_4) and the solvent was evaporated. Crystallization of the residue from diethylether/hexane afforded benzo[*d*]imidazole derivatives **56a**–**h** (64–82 %).

9.2.1. *tert*-Butyl 1-(1*H*-benzo[*d*]imidazol-2-yl)ethylcarbamate 56a

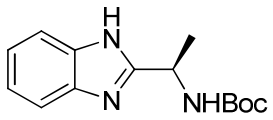


56a

The title compound was synthesized from (±)-*N*-Boc-Ala amino-amide **55a** (20.0 mmol) following the general method. White solid; yield = 4.1 g (78 %); Mp = 232–234 °C; $[\alpha]_D^{20}$ = 0 (*c* 1, MeOH); ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 12.2 (s, 1H, NH_{bim}), 7.45–7.58 (m, 2H, CH_{Ar}), 7.41 (d, *J* = 7.8 Hz, 1H, N*H*Boc), 7.17 (d, *J* = 5 Hz, 2H, CH_{Ar}), 4.88–4.93 (m, 1H, BocNHC*H*), 1.52 (d, *J* = 7.0 Hz, 3H, CH_3), 1.44 (s, 9H); ^{13}C NMR (DMSO-d_6, 100 MHz):

δ = 156.44, 155.11, 142.93, 134.28, 121.72, 120.98, 118.44, 111.28, 78.25, 45.05, 28.25, 20.17; HR-MALDI-MS (DHB): *m*/*z* $[M+H]^+$ calcd for $C_{14}H_{20}N_3O_2^+$: 262.15500; Found: 262.15419.

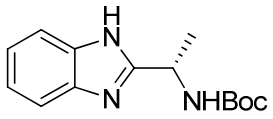
9.2.2. (*R*)-*tert*-Butyl 1-(1*H*-benzo[*d*]imidazol-2-yl)ethylcarbamate 56b



56b

The title compound was synthesized from (*R*)-*N*-Boc-Ala amino-amide **55b** (20.0 mmol) following the general method. White solid; yield = 4.3 g (82 %); Mp = 220–222 °C; $[\alpha]_D^{20}$ = +13.1 (*c* 1, MeOH); ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 12.1 (s, 1H, NH_{bim}), 7.43–7.58 (m, 2H, CH_{Ar}), 7.41 (d, *J* = 6 Hz, 1H, N*H*Boc), 7.17 (s, 2H, CH_{Ar}), 4.90 (br s, 1H, BocNHC*H*), 1.52 (d, *J* = 6.5 Hz, 3H, CH_3), 1.45 (s, 9H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 175.35, 157.06, 155.90, 155.73, 121.45, 121.12, 109.21, 108.21, 78.78, 49.45, 45.66, 28.58, 27.00, 20.78, 17.69; HR-MALDI-MS (DHB): *m*/*z* $[M+H]^+$ calcd for $C_{14}H_{20}N_3O_2^+$: 262.15500; Found: 262.15388.

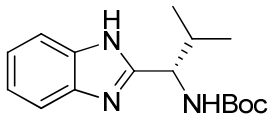
9.2.3. (*S*)-*tert*-Butyl 1-(1*H*-benzo[*d*]imidazol-2-yl)ethylcarbamate 56c



56c

The title compound was synthesized from (*S*)-*N*-Boc-Ala amino-amide **55c** (20.0 mmol) following the general method. White solid; yield = 3.94 g (75 %); Mp = 228–230 °C; $[\alpha]_D^{20}$ = −13.5 (*c* 1, MeOH); ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 12.1 (s, 1H, NH_{bim}), 7.58 (d, *J* = 6.8 Hz, 1H, CH_{Ar}), 7.48 (d, *J* = 6.8 Hz, CH_{Ar}), 7.41 (d, *J* = 7.8 Hz, 1H, N*H*Boc), 7.14–7.20 (m, 2H, CH_{Ar}), 4.86–4.93 (m, 1H, BocNHC*H*), 1.51 (d, *J* = 7.0 Hz, 3H, CH_3), 1.45 (s, 9H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 156.37, 155.05, 142.89, 134.23, 129.62, 121.68, 120.92, 118.39, 111.22, 108.43, 78.09, 44.99, 28.21, 20.11; HR-MALDI-MS (DHB): *m*/*z* $[M+H]^+$ calcd for $C_{14}H_{20}N_3O_2^+$: 262.15500; Found: 262.15504. Anal. Calcd for $C_{14}H_{19}N_3O_2$: C, 64.35; H, 7.33; N, 16.08. Found: C, 64.40; H, 7.35; N, 15.82.

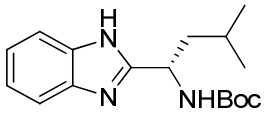
9.2.4. (*S*)-*tert*-Butyl 1-(1*H*-benzo[*d*]imidazol-2-yl)-2-methylpropylcarbamate 56d



56d

The title compound was synthesized from (*S*)-*N*-Boc-Val amino-amide **55d** (20.0 mmol) following the general method. White solid; yield = 4.12 g (71 %); Mp = 248–250 °C; $[\alpha]_D^{20}$ = −42.4 (*c* 1, MeOH); ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 12.2 (s, 1H, NH_{bim}), 7.59 (d, *J* = 7.0 Hz, 1H, CH_{Ar}), 7.50 (d, *J* = 6.5 Hz, 1H, N*H*Boc), 7.22 (d, *J* = 9 Hz, 1H, CH_{Ar}), 7.17–7.23 (m, 2H, CH_{Ar}), 4.59 (t, *J* = 8.2 Hz 1H, BocNHC*H*), 2.20–2.26 (m, 1H, C*H*$(CH_3)_2$), 1.42 (s, 9H), 0.95 (d, *J* = 6.7 Hz, 3H, CH_3), 0.83 (d, *J* = 6.7 Hz, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 155.41, 154.99, 142.90, 133.84, 124.48, 121.67, 120.96, 118.42, 111.18, 78.04, 55.15, 51.87, 32.05, 28.14, 19.28, 18.57; HR-MALDI-MS (DHB): *m*/*z* $[M+H]^+$ calcd for $C_{16}H_{24}N_3O_2^+$: 290.18630; Found: 290.18652. Anal. Calcd for $C_{16}H_{23}N_3O_2$: C, 66.41; H, 8.01; N, 14.52. Found: C, 64.66; H, 7.89; N, 13.36.

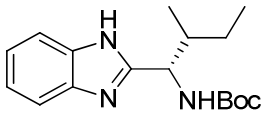
9.2.5. (*S*)-*tert*-Butyl 1-(1*H*-benzo[*d*]imidazol-2-yl)-3-methylbutylcarbamate 56e



56e

The title compound was synthesized from (*S*)-*N*-Boc-Leu amino-amide **55e** (20.0 mmol) following the general method. White solid; yield = 4.03 g (66 %); Mp = 186–188 °C; $[\alpha]_D^{20}$ = −32.3 (*c* 1, MeOH); ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 12.1 (s, 1H, NH_{bim}), 7.50–7.57 (m, 2H, CH_{Ar}), 7.34 (d, *J* = 8.5 Hz, 1H, N*H*Boc), 7.17 (d, *J* = 5,1 Hz, 2H, CH_{Ar}), 4.86 (q, *J* = 7.8 Hz, 1H, BocNHC*H*), 1.73–1.78 (m, 2H, CH_2), 1.60–1.65 (m, 1H, C*H*), 1.43 (s, 9H), 0.95 (t, *J* = 6.6 Hz, 6H, CH(CH_2)$_3$); ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 174.82, 156.22, 155.36, 121.40, 78.11, 77.94, 51.86, 47.70, 43.07, 28.25, 24.41, 22.94, 22.76, 21.84; HR-MALDI-MS (DHB): *m*/*z* $[M+H]^+$ calcd for $C_{17}H_{26}N_3O_2^+$: 304.20195; Found: 304.20100.

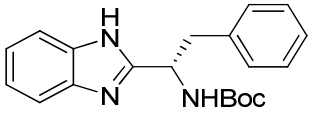
9.2.6. *tert*-Butyl (1*S*,2*S*)-1-(1*H*-benzo[*d*]imidazol-2-yl)-2-methylbutylcarbamate 56f



56f

The title compound was synthesized from (*S*)-*N*-Boc-Ile amino-amide **55f** (20.0 mmol) following the general method. Yellowish solid; yield = 4.65 g (76 %); Mp = 188–190 °C; $[\alpha]_D^{20}$ = −17.5 (*c* 1, MeOH); ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 12.2 (s, 1H, NH_{bim}), 7.55 (br s, 2H), 7.26 (d, *J* = 8.8 Hz, 1H, N*H*Boc), 7.16–7.19 (m, 2H, CH_{Ar}), 7.03 (d, *J* = 8.4 Hz, 1H, CH_{Ar}), 4.66 (t, *J* = 8.3 Hz, 1H, BocNHC*H*), 2.10–254 (m, 1H, C*H*), 1.53–1.57 (m, 1H, CH_2), 1.41 (s, 9H), 1.22–1.30 (m, 1H, CH_2), 0.88–1.01 (m, 3H, CHCH_3), 0.77 (d, *J* = 6.7 Hz, 3H, CH_2CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 155.96, 155.65, 143.59, 134.46, 122.33, 121.64, 119.09, 111.86, 78.72, 54.55, 38.95, 28.82, 28.60, 25.46, 16.22, 11.95, 11.65; HR-MALDI-MS.(DHB): *m*/*z* $[M+H]^+$ calcd for $C_{17}H_{26}N_3O_2^+$: 304.20195; Found: 304.20152.

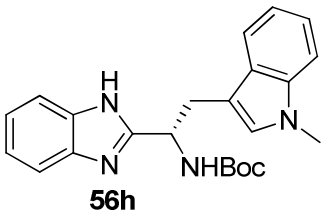
9.2.7. (*S*)-*tert*-Butyl 1-(1*H*-benzo[*d*]imidazol-2-yl)-2-phenylethylcarbamate 56g



56g

The title compound was synthesized from (*S*)-*N*-Boc-Phe amino-amide **55g** (20.0 mmol) following the general method. White solid; yield = 5.35 g (79 %); Mp = 180–182 °C; $[\alpha]_D^{20}$ = −10.4 (*c* 1, MeOH); ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 12.28 (br s, 1H, NH_{bim}), 7.56 (br, s, 1H, N*H*Boc), 7.44 (d, *J* = 8.7 Hz, 1H, CH_{Ar}), 7.22–7.29 (m, 4H, CH_{Ar}), 7.17–7.19 (m, 3H, CH_{Ar}), 5.01–5.07 (m, 1H, BocNHC*H*), 2.78–3.22 (m, 2H, CHCH_2Ph, 1.34 (s, 9H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 155.92, 155.80, 143.59, 138.80, 134.78, 129.86, 128.70, 126.83, 122.45, 121.68, 119.15, 111.96, 78.70, 51.48, 28.80; HR-MALDI-MS (DHB): *m*/*z* $[M+H]^+$ calcd for $C_{20}H_{24}N_3O_2^+$: 338.18630; Found: 338.18640. Anal. Calcd for $C_{20}H_{23}N_3O_2$: C, 71.19; H, 6.87; N, 12.45. Found: C, 69.10; H, 6.74; N, 10.36.

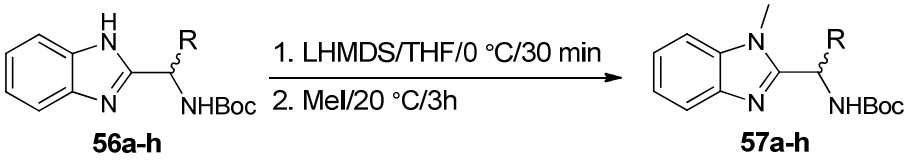
9.2.8. (*S*)-*tert*-Butyl 1-(1*H*-benzo[*d*]imidazol-2-yl)-2-(1-methyl-1*H*-indol-3-yl)ethylcarbamate 56h



56h

The title compound was synthesized from (*S*)-*N*-Boc-1-MeTrp amino-amide **55h** (20.0 mmol) following the general method. Yellowish solid; yield = 5.0 g (64 %); Mp = 204–206 °C; $[\alpha]_D^{20}$ = −30.5 (*c* 1, MeOH); ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 12.2 (s, 1H), 7.48–7.64 (m, 3H, CH_{Ar}), 7.39 (t, *J* = 9.5 Hz, 1H), 7.15–7.22 (m, 3H, CH_{Ar}), 7.02–7.05 (m, 2 H, CH_{Ar}) 5.81 (s, 1H), 5.08 (q, *J* = 7.5 Hz, 1H, BocNHC*H*), 3.73 (s, 3H, NCH_3), 3.48 (dd, *J* = 14.5, 5.7 Hz, 1H, CHCH_2Try), 3.24 (dd, *J* = 14.5, 8.7 Hz, 1H, CHCH_2Try), 1.36 (s, 9H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 155.61, 155.27, 143.03, 136.49, 134.20, 127.85, 127.76, 121.80, 121.05, 121.03, 118.68, 118.54, 118.39, 111.34, 109.90, 109.54, 78.07, 50.41, 32.31, 29.76, 28.18; HR-MALDI-MS (DHB): *m*/*z* $[M+H]^+$ calcd for $C_{23}H_{27}N_4O_2^+$: 391.21285; Found: 391.21269.

9.3 General procedure for the synthesis *N*-substituted benzo[*d*]imidazole



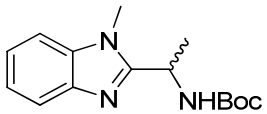
56a-h **57a-h**

57a, R = Me (±) **57e,** R = *i*-Bu (*S*)
57b, R = Me (*R*) **57f,** R = *s*-Bu (*S*)
57c, R = Me (*S*) **57g,** R = CH_2Ph (*S*)
57d, R = *i*-Pr (*S*) **57h,** R = (1-Methylindol-3-yl)methyl (*S*)

Scheme 28. *Synthesis of N-methyl benzo*[*d*]*imidazole linked with Boc protected α-amino acids.*

Benzimidazoles **56a**–**h** (3.8 mmol) dissolved in dry THF (20 mL) were treated with LHMDS (3.8 mL, 3.8 mmol, 1M sol. in THF) at 0 °C for 30 min, whereupon iodomethane (0.25 mL, 4.0 mmol) was added and the reaction was stirred at 20 °C for 3 h. The reaction was diluted with water and extracted with EtOAc. Organic layer was dried (Na_2SO_4), the solvents were evaporated, and the residue was purified by column chromatography (SiO_2; EtOAc/Hexane 1:1) to afford *N*-methyl derivatives **57a**–**h** (50–86 %).

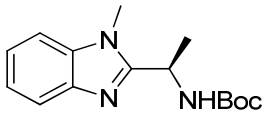
9.3.1. *tert*-Butyl 1-(1-methyl-1*H*-benzo[*d*]imidazol-2-yl)ethylcarbamate 57a



57a

The title compound was synthesized from (±)-*N*-Boc-Ala BIM **56a** (3.8 mmol) following the general method. White solid; yield = 0.9 g (86 %); R_f 0.5; Mp = 134–136 °C; $[\alpha]_D^{20}$ = 0 (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.78–7.92 (m, 1H), 7.29–7.40 (m, 3H C*H*$_{Ar}$), 5.56 (d, *J* = 8.5 Hz, 1H, N*H*Boc), 5.19–5.26 (m, 1H, BocNHC*H*), 3.86 (s, 3H, NC*H*$_3$), 1.69 (d, *J* = 6.8 Hz, 3H, C*H*$_3$), 1.49 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 155.58, 155.27, 142.22, 135.94, 122.88, 122.37, 119.65, 109.54, 80.03, 42.99, 29.97, 28.52, 21.02; HR-MALDI-MS (DHB): *m*/*z* $[M+H]^+$ calcd for $C_{15}H_{22}N_3O_2^+$: 276.17065; Found: 276.16979.

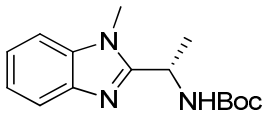
9.3.2. (*R*)-*tert*-Butyl 1-(1-methyl-1*H*-benzo[*d*]imidazol-2-yl)ethylcarbamate 57b



57b

The title compound was synthesized from (*R*)-*N*-Boc-Ala BIM **56b** (3.8 mmol) following the general method. Yellowish solid; yield = 0.8 g (76 %); R_f 0.5; Mp = 138–140 °C; $[\alpha]_D^{20}$ = +84.1 (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.77–7.80 (m, 1H, C*H*$_{Ar}$), 7.29–7.40 (m, 3H C*H*$_{Ar}$), 5.61 (d, *J* = 8.7 Hz, 1H, N*H*Boc), 5.19–5.26 (m, 1H, BocNHC*H*), 3.85 (s, 3H, NC*H*$_3$), 1.69 (d, *J* = 6.8 Hz, 3H, C*H*$_3$), 1.50 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 155.55, 155.25, 142.15, 135.89, 122.85, 122.33, 119.60, 109.53, 80.00, 42.95, 29.95, 28.49, 20.98; HR-MALDI-MS (DHB): *m*/*z* $[M+H]^+$ calcd for $C_{15}H_{22}N_3O_2^+$: 276.17065; Found: 276.16956.

9.3.3. (*S*)-*tert*-Butyl 1-(1-methyl-1*H*-benzo[*d*]imidazol-2-yl)ethylcarbamate 57c

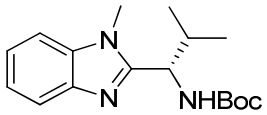


57c

The title compound was synthesized from (*S*)-*N*-Boc-Ala BIM **56c** (3.8 mmol) following the general method. Red solid; yield = 0.695 g (66 %); R_f 0.5; Mp = 128–130 °C; $[\alpha]_D^{20}$ = −84.8 (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.71–7.84 (m, 1H), 7.22–7.33 (m, 3H C*H*$_{Ar}$), 5.49 (d, *J* = 8.6 Hz, 1H, N*H*Boc), 5.12–5.19 (m, 1H, BocNHC*H*), 3.79 (s, 3H,

NC*H*$_3$), 1.62 (d, *J* = 6.8 Hz, 3H, C*H*$_3$), 1.42 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 155.58, 155.29, 142.23, 135.96, 122.89, 122.38, 119.67, 109.56, 80.06, 43.02, 29.98, 28.54, 21.05; HR-MALDI-MS (DHB): *m*/*z* $[M+H]^+$ calcd for $C_{15}H_{22}N_3O_2^+$: 276.17065; Found: 276.16937.

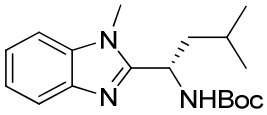
9.3.4. (*S*)-*tert*-Butyl 2-methyl-1-(1-methyl-1*H*-benzo[*d*]imidazol-2-yl)propylcarbamate 57d



57d

The title compound was synthesized from (*S*)-*N*-Boc-Val BIM **56d** (3.8 mmol) following the general method. Yellow solid; yield = 0.665 g (58 %); R_f 0.7; Mp = 114–116 °C; $[\alpha]_D^{20}$ = −62.1 (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.15 (s, 1H), 7.78–7.80 (m, 1H, C*H*$_{Ar}$), 7.33–7.42 (m, 2H, C*H*$_{Ar}$), 5.49 (d, *J* = 9.6 Hz, 1H, BocN*H*CH), 4.86 (t, *J* = 5.8 Hz 1H, BocNHC*H*), 3.89 (s, 3H, NC*H*$_3$), 2.30–2.39 (m, 1H, C*H*$(CH_3)_2$), 1.48 (s, 9H), 1.12 (d, *J* = 6.7 Hz, 3H, C*H*$_3$), 0.99 (d, *J* = 6.7 Hz, 3H, C*H*$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 155.91, 155.23, 142.47, 135.53, 122.69, 122.37, 119.57, 109.68, 79.87, 52.47, 33.66, 30.18, 28.51, 19.77, 18.58; HR-MALDI-MS (DHB): *m*/*z* $[M+H]^+$ calcd for $C_{17}H_{26}N_3O_2^+$: 304.20195; Found: 304.20202. Anal. Calcd for $C_{17}H_{25}N_3O_2$: C, 67.30; H, 8.31; N, 13.85. Found: C, 67.21; H, 8.30; N, 13.67.

9.3.5. (*S*)-*tert*-Butyl 3-methyl-1-(1-methyl-1*H*-benzo[*d*]imidazol-2-yl)butylcarbamate 57e

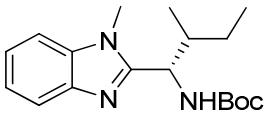


57e

The title compound was synthesized from (*S*)-*N*-Boc-Leu BIM **56e** (3.8 mmol) following the general method. White solid; yield = 0.793 g (65 %); R_f 0.6; Mp = 102–104 °C; $[\alpha]_D^{20}$ = −41 (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.71–7.73 (m, 1H, C*H*$_{Ar}$), 7.22–7.34 (m, 1H, C*H*$_{Ar}$), 7.23–7.29 (m, 2H, C*H*$_{Ar}$), 5.19 (d, *J* = 9.3 Hz, 1H, N*H*Boc), 5.12–5.14 (m, 1H, BocNHC*H*), 3.83 (s, 3H, NC*H*$_3$), 1.86–1.90 (m, 2H, C*H*$_2$), 1.70–1.74 (m, 1H, C*H*), 1.40 (s, 9H), 0.99 (d, *J* = 6.5 Hz, 3H, CH(C*H*$_2$)$_3$), 0.95 (d, *J* = 6.6 Hz, 3H, CH(C*H*$_2$)$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 155.80, 135.68, 134.61, 129.62, 122.78, 122.35, 119.66, 109.64, 79.99, 45.10, 44.29, 30.03, 28.51, 24.93, 23.13, 22.44; HR-MALDI-MS (DHB): *m*/*z* $[M+H]^+$ calcd

for $C_{18}H_{28}N_3O_2^+$: 318.21760; Found: 318.21729. Anal. Calcd for $C_{18}H_{27}N_3O_2$: C, 68.11; H, 8.57; N, 13.24. Found: C, 67.91; H, 8.54; N, 13.16.

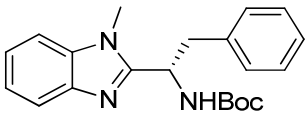
9.3.6. *tert*-Butyl (1*S*,2*S*)-2-methyl-1-(1-methyl-1*H*-benzo[*d*]imidazol-2-yl)butylcarbamate 57f



57f

The title compound was synthesized from (*S*)-*N*-Boc-Ile BIM **56f** (3.8 mmol) following the general method. Yellow solid; yield = 0.780 g (64.00 %); R_f 0.5; Mp = 104–106 °C; $[\alpha]_D^{20}$ = −73.5 (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.71–7.73 (m, 1H, C*H*$_{Ar}$), 7.33–7.35 (m, 1H, C*H*$_{Ar}$), 7.23–7.29 (m, 2H, C*H*$_{Ar}$), 5.39 (d, *J* = 9.5 Hz, 1H, N*H*Boc), 4.82 (t, *J* = 9.0 Hz, 1H, BocNHC*H*), 3.82 (s, 3H, NC*H*$_3$), 2.01–2.08 (m, 1H, C*H*), 1.71–1.76 (m, 1H, C*H*$_2$), 1.39 (s, 9H), 1.20–1.24 (m, 1H, C*H*$_2$), 0.91 (t, *J* = 7.4 Hz, 3H, CHC*H*$_3$), 0.85 (d, *J* = 6.7 Hz, 3H, CH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 155.84, 155.45, 142.53, 135.46, 122.66, 122.37, 119.56, 109.72, 79.88, 51.51, 39.95, 30.20, 28.51, 24.99, 15.97, 11.40; HR-MALDI-MS (DHB): *m*/*z* $[M+H]^+$ calcd for $C_{18}H_{28}N_3O_2^+$: 318.21760; Found: 318.21717. Anal. Calcd for $C_{18}H_{27}N_3O_2$: C, 68.11; H, 8.57; N, 13.24. Found: C, 67.91; H, 8.75; N, 13.12.

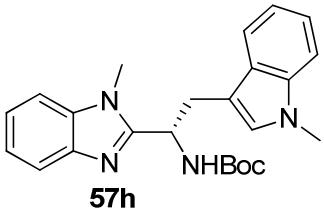
9.3.7. (*S*)-*tert*-Butyl 1-(1-methyl-1*H*-benzo[*d*]imidazol-2-yl)-2-phenylethylcarbamate 57g



57g

The title compound was synthesized from (*S*)-*N*-Boc-Phe BIM **56g** (3.8 mmol) following the general method. White solid; yield = 0.666 g (50 %); R_f 0.8; Mp = 132–134 °C; $[\alpha]_D^{20}$ = −18.8 (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.80–7.83 (m, 1H, C*H*$_{Ar}$), 7.23–7.34 (m, 8H, C*H*$_{Ar}$), 7.07–7.09 (m, 1H, C*H*$_{Ar}$), 5.72 (d, J = 8.8 Hz, 1H, N*H*Boc), 5.21–5.27 (m, 1H, BocNHC*H*), 3.43–3.55 (m, 2H, C*H*CH$_2$Ph), 3.33 (s, 3H, NC*H*$_3$), 1.47 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 154.56, 142.43, 136.90, 129.62, 128.65, 127.03, 122.77, 122.41, 119.55, 109.55, 49.14, 42.73, 29.40, 28.52; HR-MALDI-MS (DHB): *m*/*z* $[M+H]^+$ calcd for $C_{21}H_{26}N_3O_2^+$: 352.20195; Found: 352.20187.

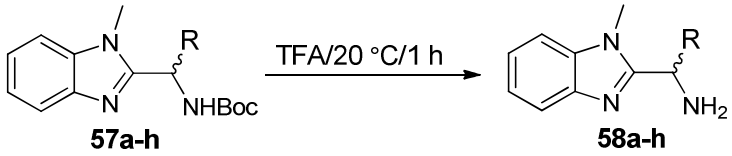
9.3.8. (*S*)-*tert*-Butyl 1-(1-methyl-1*H*-benzo[*d*]imidazol-2-yl)-2-(1-methyl-1*H*-indol-3-yl)ethylcarbamate 57h



57h

The title compound was synthesized from (*S*)-*N*-Boc-1-MeTrp BIM **56h** (3.8 mmol) following the general method. Brown solid; yield = 0.991 g (64 %); R_f 0.5; Mp = 164–166 °C; $[\alpha]_D^{20}$ = −20.1 (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.75 (d, *J* = 7.5 Hz, 1H, C*H*$_{Ar}$), 7.49 (d, *J* = 7.8 Hz, 1H, C*H*$_{Ar}$), 7.15–7.28 (m, 6H, C*H*$_{Ar}$), 6.99 (t, *J* = 7.5 Hz, 1H, C*H*$_{Ar}$), 6.66 (s, 1H, N*H*Boc), 5.78 (br s, 1H), 5.34 (q, *J* = 7.8 Hz, 1H, BocNHC*H*), 3.61 (s, 3H, NC*H*$_3$), 3.54 (dd, *J* = 14.0, 5.4 Hz, 1H, CHC*H*$_2$Try), 3.40 (dd, *J* = 14.0, 9.4 Hz, 1H, CHC*H*$_2$Try), 3.20 (s, 3H, NC*H*$_3$), 1.41 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 155.49, 155.36, 136.98, 135.32, 129.94, 128.10, 127.82, 122.78, 122.51, 121.83, 119.34, 118.98, 109.73, 109.41, 109.29, 79.99, 48.13, 32.82, 32.16, 29.75, 28.54; HR-MALDI-MS (DHB): *m*/*z* $[M+H]^+$ calcd for $C_{24}H_{29}N_4O_2^+$: 405.22850; Found: 405.22849.

9.4 General procedure for the synthesis benzo[*d*]imidazole linked with primary amine



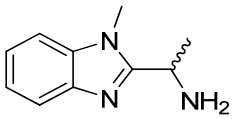
57a-h **58a-h**

58a, R = Me (±) **58e,** R = *i*-Bu (*S*)
58b, R = Me (*R*) **58f,** R = *s*-Bu (*S*)
58c, R = Me (*S*) **58g,** R = CH_2Ph (*S*)
58d, R = *i*-Pr (*S*) **58h,** R = (1-Methylindol-3-yl)methyl (*S*)

Scheme 29. *Synthesis of N-methyl benzo[d]imidazole linked with primary amine.*

Boc-derivatives **57a**–**h** (2.3 mmol) were treated with TFA (1 mL) at 20 °C for 1 h. Diethylether/hexane (1:1) was added to the reaction mixture until the product precipitated. The crude product was filtered and purified by column chromatography (SiO_2; EtOAc/DCM/MeOH 1:1:0.2) to afford **58a**–**h** as viscose oils (36–61 %).

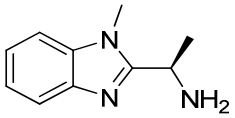
9.4.1. 1-(1-Methyl-1*H*-benzo[*d*]imidazol-2-yl)ethanamine 58a



58a

The title compound was synthesized from (±)-*N*-Boc-Ala BIM-*N*-Me **57a** (2.3 mmol) following the general method. Yellow oil; yield = 0.185 g (45 %); R_f 0.2; $[\alpha]_D^{20}$ = 0 (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.71–7.73 (m, 1H, CH_{Ar}), 7.22–7.32 (m, 3H CH_{Ar}), 4.33 (q, *J* = 6.7 Hz, 1H, NH_2C*H*), 3.79 (s, 3H, NCH_3), 1.57 (d, *J* = 6.7 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 159.09, 141.76, 136.06, 121.64, 121.19, 118.59, 109.79, 43.64, 29.62, 23.34, 23.04; IR (HATR): ν_{max} = 3100, 3050, 2998, 1681, 1479, 1458, 1335, 1258, 1128, 742 cm^{-1}; HR-MALDI-MS (DHB): *m*/*z* $[M+H]^+$ calcd for $C_{10}H_{14}N_3^+$: 176.11877; Found: 176.11746.

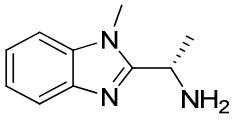
9.4.2. (*R*)-1-(1-Methyl-1*H*-benzo[*d*]imidazol-2-yl)ethanamine 58b



58b

The title compound was synthesized from (*R*)-*N*-Boc-Ala BIM-*N*-Me **57b** (2.3 mmol) following the general method. Yellow oil; yield = 0.197 g (48 %); R_f 0.2; $[\alpha]_D^{20}$ = +4.0 (*c* 1, MeOH); ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 7.61 (d, *J* = 7.4 Hz, 1H, CH_{Ar}), 7.54 (d, , *J* = 7.5 Hz , 1H, CH_{Ar}), 7.18–7.27 (m, 2H, CH_{Ar}) 4.33 (q, *J* = 6.7 Hz, 1H, NH_2C*H*), 3.86 (s, 3H, NCH_3), 1.49 (d, *J* = 6.5 Hz, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 158.91, 141.76, 136.06, 121.67, 121.22, 118.60, 109.82, 43.62, 29.63, 22.93; IR (HATR): ν_{max} = 3100, 3050, 2932, 1684, 1630, 1456, 1395, 1331, 740 cm^{-1}; HR-MALDI-MS (DHB): *m*/*z* $[M+H]^+$ calcd for $C_{10}H_{14}N_3^+$: 176.11877; Found: 176.11765.

9.4.3. (*S*)-1-(1-Methyl-1*H*-benzo[*d*]imidazol-2-yl)ethanamine 58c

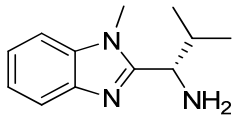


58c

The title compound was synthesized from (*S*)-*N*-Boc-Ala BIM-*N*-Me **57c** (2.3 mmol) following the general method. Yellow oil; yield = 0.184 g (45 %); R_f 0.2; $[\alpha]_D^{20}$ = −4.2 (*c* 1, MeOH); ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 7.61 (d, *J* = 7.4 Hz, 1H, CH_{Ar}), 7.54 (d, *J* = 7.4

Hz , 1H, C*H*$_{Ar}$), 7.14–7.27 (m, 2H, C*H*$_{Ar}$) 4.31 (q, *J* = 6.7 Hz, 1H, NH$_2$C*H*), 3.86 (s, 3H, NC*H*$_3$), 1.49 (d, *J* = 6.6 Hz, 3H, C*H*$_3$); ^{13}C NMR (DMSO-*d*$_6$, 100 MHz): δ = 159.10, 141.75, 136.05, 121.61, 121.16, 118.57, 109.77, 43.63, 29.61, 23.05; IR (HATR): ν_{max} = 3100, 3030, 2933, 1680, 1457, 1335, 1128, 741 cm^{-1}; HR-MALDI-MS (DHB): *m*/*z* [M+H]$^+$ calcd for $C_{10}H_{14}N_3^+$: 176.11877; Found: 176.11816.

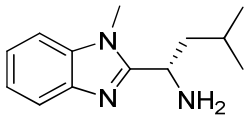
9.4.4. (*S*)-2-Methyl-1-(1-methyl-1*H*-benzo[*d*]imidazol-2-yl)propan-1-amine 58d



58d

The title compound was synthesized from (*S*)-*N*-Boc-Val BIM-*N*-Me **57d** (2.3 mmol) following the general method. Yellow solid; yield = 0.287 g (61 %); R_f 0.3; Mp = 80–82 °C; $[\alpha]_D^{20}$ = −11.4 (*c* 1, MeOH); ^{1}H NMR (DMSO-*d*$_6$, 500 MHz): δ = 7.61 (d, *J* = 7.4 Hz, 1H, C*H*$_{Ar}$), 7.55 (d, *J* = 7.7 Hz, 1H, C*H*$_{Ar}$), 7.19–7.26 (m, 2H, C*H*$_{Ar}$), 3.90 (d, *J* = 7.0 Hz, 1H, NH$_2$C*H*), 3.84 (s, 3H, NC*H*$_3$), 2.05–2.13 (m, 1H, C*H*(CH$_3$)$_2$), 1.01 (d, *J* = 6.7 Hz, 3H, C*H*$_3$), 0.88 (d, *J* = 6.7 Hz, 3H, C*H*$_3$); ^{13}C NMR (DMSO-*d*$_6$, 125 MHz): δ = 158.25, 141.93, 135.75, 121.55, 121.28, 118.52, 109.97, 53.52, 33.33, 29.76, 19.87, 18.23; IR (HATR): ν_{max} = 3060, 2961, 2860, 1683, 1612, 1467, 1200, 1126, 740 cm^{-1}; HR-MALDI-MS (DHB): *m*/*z* [M+H]$^+$ calcd for $C_{12}H_{18}N_3^+$: 204.14952; Found: 204.14897.

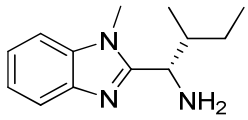
9.4.5. (*S*)-3-Methyl-1-(1-methyl-1*H*-benzo[*d*]imidazol-2-yl)butan-1-amine 58e



58e

The title compound was synthesized from (*S*)-*N*-Boc-Leu BIM-*N*-Me **57e** (2.3 mmol) following the general method. Viscous oil; yield = 0.195 g (39 %); R_f 0.2; $[\alpha]_D^{20}$ = −15 (*c* 1, MeOH); ^{1}H NMR (DMSO-*d*$_6$, 500 MHz): δ = 7.61 (d, *J* = 7.7 Hz, 1H, C*H*$_{Ar}$), 7.55 (d, *J* = 7.9 Hz, 1H, C*H*$_{Ar}$), 7.19–7.27 (m, 2H, C*H*$_{Ar}$), 4.23 (t, *J* = 6.8 Hz, 1H, NH$_2$C*H*), 3.86 (s, 3H, NC*H*$_3$), 1.75–1.78 (m, 2H, C*H*$_2$), 1.67–1.72 (m, 1H, C*H*), 0.93 (d, *J* = 6.0 Hz, 6H, CH(C*H*$_3$)$_2$); ^{13}C NMR (DMSO-*d*$_6$, 125 MHz): δ = 158.39, 141.86, 135.97, 121.79, 121.39, 118.63, 110.00, 46.14, 45.52, 29.75, 24.43, 23.06, 22.29; IR (HATR): ν_{max} = 3030, 3040, 2958, 2810, 1678, 1454, 1201, 1133, 746 cm^{-1}; HR-MALDI-MS (DHB): *m*/*z* [M+H]$^+$ calcd for $C_{13}H_{20}N_3^+$: 218.16517; Found: 218.16497.

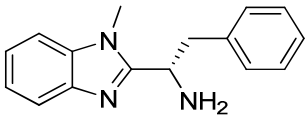
9.4.6. (1*S*,2*S*)-2-Methyl-1-(1-methyl-1*H*-benzo[*d*]imidazol-2-yl)butan-1-amine 58f



58f

The title compound was synthesized from (*S*)-*N*-Boc-Ile BIM-*N*-Me **57f** (2.3 mmol) following the general method. Viscous oil; yield = 0.180 g (36 %); R_f 0.2; $[\alpha]_D^{20}$ = −21.8 (*c* 1, MeOH); ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 7.62 (d, *J* = 7.0 Hz, 1H, C*H*$_{Ar}$), 7.56 (d, *J* = 7.0 Hz, 1H, C*H*$_{Ar}$), 7.20–7.55 (m, 2H, C*H*$_{Ar}$), 4.03 (d, *J* = 7.6 Hz, 1H, NH$_2$C*H*), 3.85 (s, 3H, NC*H*$_3$), 1.88–1.90 (m, 1H, C*H*), 1.19 and 1.75 (2 × m, 2 × 1H, C*H*$_2$), 0.90 (t, *J* = 7.2 Hz, 3H, CHC*H*$_3$), 0.85 (d, *J* = 6.4 Hz, 3H, CH$_2$C*H*$_3$); ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 157.67, 141.92, 135.68, 121.62, 121.35, 118.51, 110.02, 52.30, 39.92, 29.80, 24.06, 15.78, 11.20; IR (HATR): ν_{max} = 3330, 3250, 2965, 1678, 1558, 1471, 1202, 1180, 1130, 744, 721 cm^{-1}; HR-MALDI-MS (DHB): *m*/*z* [M+H]$^+$ calcd for $C_{13}H_{20}N_3^+$: 218.16517; Found: 218.16473.

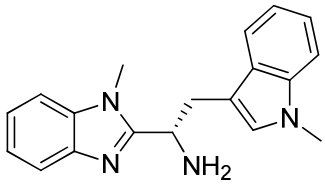
9.4.7. (*S*)-1-(1-Methyl-1*H*-benzo[*d*]imidazol-2-yl)-2-phenylethanamine 58g



58g

The title compound was synthesized from (*S*)-*N*-Boc-Phe BIM-*N*-Me **57g** (2.3 mmol) following the general method. Oil; yield = 0.220 g (38 %), R_f 0.3; $[\alpha]_D^{20}$ = −6.2 (*c* 1, MeOH, 20 % ee); ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 7.82–7.85 (m, 1H, C*H*$_{Ar}$), 7.27–7.35 (m, 6H, C*H*$_{Ar}$), 7.13–7.15 (m, 2H, C*H*$_{Ar}$), 4.44 (t, J = 7.2 Hz, 1H, NH$_2$C*H*), 3.45 (s, 3H, NC*H*$_3$), 3.23–3.34 (m, 2H, C*H*CH$_2$Ph); ^{13}C NMR (CDCl$_3$, 100 MHz): δ = 157.04, 142.19, 137.79, 129.53, 128.84, 127.07, 122.71, 122.39, 119.56, 109.46, 50.96, 44.77, 29.58; IR (HATR): ν_{max} = 3100, 3050, 2926, 1676, 1460, 1261, 1122, 733, 698 cm^{-1}; HR-MALDI-MS (DHB): *m*/*z* [M+H]$^+$ calcd for $C_{16}H_{18}N_3^+$: 252.14952; Found: 252.14904.

9.4.8. (*S*)-1-(1-Methyl-1*H*-benzo[*d*]imidazol-2-yl)-2-(1-methyl-1*H*-indol-3-yl)ethanamine 58h



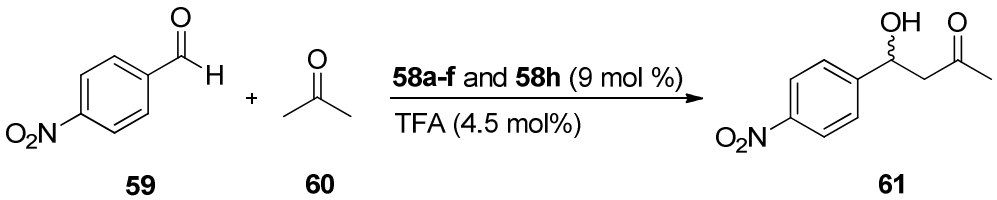
58h

The title compound was synthesized from (*S*)-*N*-Boc-1-MeTrp BIM-*N*-Me **4h** (2.3 mmol) following the general method. Yellow oil; yield = 0.377 g (53 %); R_f 0.2; $[\alpha]_D^{20}$ = −7.5 (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.80–7.85 (m, 1H, C*H*$_{Ar}$), 7.53 (d, *J* = 7.8 Hz, 1H, C*H*$_{Ar}$), 7.22–7.32 (m, 4H, C*H*$_{Ar}$), 7.08 (t, *J* = 7.4 Hz, 1H, C*H*$_{Ar}$), 6.86 (s, 1H), 4.51 (t, *J* = 7.1 Hz, 1H, , NH_2C*H*), 3.73 (s, 3H, NC*H*$_3$), 3.56 (s, 3H, NC*H*$_3$), 3.45 (dd, *J* = 16.0, 7.1 Hz, 1H, CHC*H*$_2$Try), 3.35 (dd, *J* = 14.2, 8.2 Hz, 1H, CHC*H*$_2$Try); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 157.41, 142.13, 137.24, 135.90, 128.24, 127.91, 122.67, 122.34, 121.94, 119.58, 118.70, 110.08, 109.39, 109.04, 49.66, 33.92, 32.87, 31.94, 29.88; IR (HATR): ν_{max} = 3070, 2924, 1612, 1520, 1470, 1326, 1123, 1006, 844, 738 cm^{-1}; HR-MALDI-MS (DHB): *m*/*z* $[M+H]^+$ calcd for $C_{19}H_{21}N_4^+$: 305.17783; Found: 305.17652.

9.5 General procedure for the aldol reaction of 4-nitrobenzaldehyde with ketones

A solution of catalyst **58a**–**f** and **58h** (0.09 mmol) in acetone or cyclohexanone (7.5 mL) was treated with TFA (3.5 μL, 0.045 mmol) at 20 °C for 5 min, whereupon 4-nitrobenzaldehyde (151 mg, 1.0 mmol) was added and the reaction was stirred for 24 h or 72 h. The progress of the reaction was monitored by TLC. The solvent was evaporated and the residue was purified by column chromatography (SiO_2; EtOAc/hexane 1:1). to afford aldol products **61** or **63** as a pale yellow solid.

9.5.1. Asymmetric aldol reaction of 4-nitrobenzaldehyde with acetone



59 **60** **61**

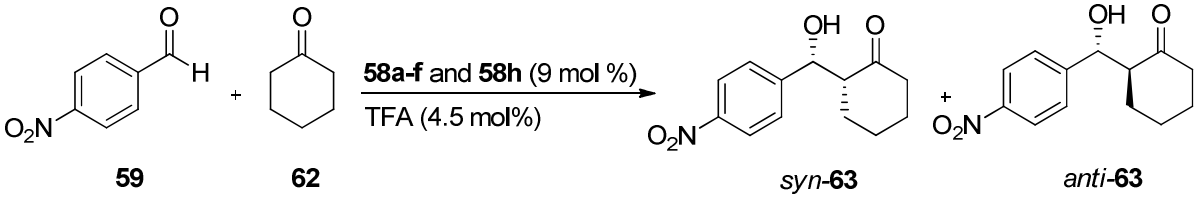
Scheme 30. *Asymmetric aldol reaction of 4-nitrobenzaldehyde with acetone.*

The enantiomeric excess of the aldol product **61** was determined by HPLC analysis (Daicel Chiralpak AS-H, flow 0.5 mL.min^{-1}, *n*-hexane/*i*-PrOH 70:30; t_{maj} 25.13 min, t_{min} 30.10 min, 65 % *ee* for the reaction catalyzed by **58f**).[43,44]

Table 7. Aldol reaction of 4-nitrobenzaldehyde with acetone.

Catalyst	Yield [%]	*ee* [%]	Configuration
58a	51	0	±
58b	40	32	*S*
58c	46	32	*R*
58d	48	49	*R*
58e	51	59	*R*
58f	59	65	*R*
58h	51	3	*R*

9.5.2. Asymmetric aldol reaction of 4-nitrobenzaldehyde with cyclohexanone



Scheme 31. *Asymmetric aldol reaction of 4-nitrobenzaldehyde with cyclohexanone.*

The enantiomeric excess of the aldol product **63** was determined by HPLC analysis (Daicel Chiralpak AD-H column, flow 0.5 mL.min^{-1}, *n*-hexane/*i*-PrOH 80:20; Major diastereoisomer: t_{maj} 32.57 min, t_{min} 25.78 min, 62 % *ee* for the reaction catalyzed by **58d**; minor diastereoisomer: t_{maj} 22.4 min, t_{min} 23.66 min, 32 % *ee* for the reaction catalyzed by **58d**).[45]

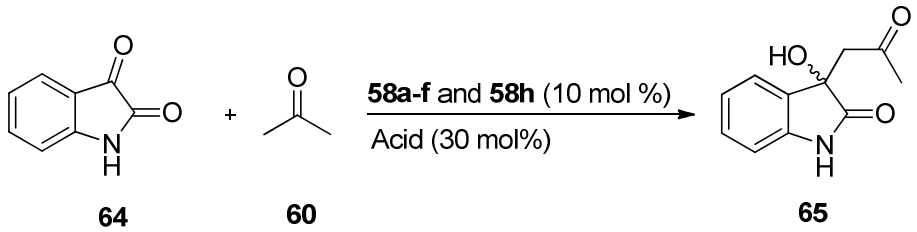
Table 8. Aldol reaction of 4-nitrobenzaldehyde with cyclohexanone.

Catalyst	Yield [%]	*syn*:*anti*/*de*	*ee syn* [%]	*ee anti* [%]
58a	48	2:98/96	0	0
58b	46	3:97/94	32 (2*S*,1'*S*)	29(2*R*,1'*S*)
58c	49	17:83/66	23(2*R*,1'*R*)	32(2*S*,1'*R*)
58d	51	7:93/86	32(2*R*,1'*R*)	62(2*S*,1'*R*)
58e	60	4:96/92	23(2*R*,1'*R*)	32(2*S*,1'*R*)
58f	64	8:92/84	31(2*R*,1'*R*)	39(2*S*,1'*R*)
58h	49	12:88/76	10(2*R*,1'*R*)	36(2*S*,1'*R*)

9.6 General procedure for the aldol reaction of isatins with ketones

A solution of catalyst **58a**–**f** and **58h** (0.01 mmol) in acetone or cyclohexanone (1 mL) was treated with benzoic acid (0.03 mmol) at 5 °C, whereupon isatin (0.10 mmol) was added and the mixture was stirred for 96 or 108 h. The progress of the reaction was monitored by TLC. The acetone was subsequently removed in vacuo and the mixture was purified by column chromatography (SiO_2: EtOAc\hexane, 1:1) to afford aldol product **65** as a pale yellow solid. The crude reaction mixture after the reaction with cyclohexanone was subjected directly to column chromatography (SiO_2: EtOAc-hexane, 1:1) to afford aldol product **66** as a pale yellow solid.

9.6.1. Asymmetric aldol reaction of isatin with acetone



Scheme 32. *Asymmetric aldol reaction of isatin with acetone.*

The enantiomeric excess of the aldol product **65** was determined by HPLC analysis (Daicel Chiralcel OJ-H column, flow 0.8 mL.min^{-1}, *n*-hexane/*i*-PrOH 80:20; t_{maj} 24.6 min, t_{min} 22.0 min, 24 % *ee* for the reaction catalyzed by **58f**). ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 10.2 (s, 1H), 7.28 (d, J = 7.4 Hz, 1H), 7.22 (dt, J_t = 7.6 Hz, J_d = 1.3 Hz, 1H), 6.95 (dt, J_t = 7.5 Hz, J_d = 1.0 Hz, 1H), 6.82 (d, J = 7.6 Hz, 1H), 6.03 (s, 1H), 3.32 (d, J = 16.6 Hz, 1H), 3.04 (d, J = 16.6 Hz, 1H), 2.04 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 205.86, 178.81, 143.14, 132.12, 129.63, 124.30, 121.89, 110.07, 73.27, 50.86, 31.18; HR-MALDI-MS (DHB): *m*/*z* $[M+Na]^+$ calcd for $C_{11}H_{11}NNaO_3^+$: 228.06311; Found: 228.06326. The absolute configuration of the title compound was assigned as *S*, by comparison of chiral phase HPLC analysis with the reported data.[46]

Table 9. Aldol reaction of isatin with acetone.

Catalyst	Acid	Yield [%]	*ee* [%]	Configuration
58a	$PhCO_2H$	56	0	±
58b	TFA	58	1	*R*
58b	AcOH	64	2	*R*
58b	$PhCO_2H$	65	4	*R*
58c	TFA	64	1	*S*
58c	AcOH	66	2	*S*
58c	$PhCO_2H$	68	4	*S*

58d	TFA	57	3	*S*
58d	AcOH	59	5	*S*
58d	$PhCO_2H$	67	6	*S*
58e	TFA	62	12	*S*
58e	AcOH	64	15	*S*
58e	$PhCO_2H$	74	16	*S*
58f	TFA	67	18	*S*
58f	AcOH	72	22	*S*
58f	$PhCO_2H$	70	24	*S*
58h	TFA	61	1	*S*
58h	AcOH	62	1	*S*
58h	$PhCO_2H$	66	3	*S*

9.6.2. Asymmetric aldol reaction of isatin with cyclohexanone

Scheme 33. *Asymmetric aldol reaction of isatin with cyclohexanone.*

The enantiomeric excess of the aldol product **66** was determined by HPLC analysis (Daicel Chiralcel OJ-H column, flow 0.8 mL.min^{-1}, *n*-hexane/*i*-PrOH 85:15; Major diastereoisomer: t_{maj} 21.2 min, t_{min} 28.1 min, 71 % *ee* for the reaction catalyzed by **58f**; minor diastereoisomer: t_{maj} 16.7 min, t_{min} 18.6 min, 45 % *ee* for the reaction catalyzed by **58f**). ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 10.19 (s, 1H), 7.12–7.20 (m, 1H), 6.73–6.84 (m, 2H), 5.81 (s, 1H), 3.05 (dd, J = 13.2, 5.2 Hz, 1H), 2.55–2.58 (m, 1H), 2.25–2.31 (m, 1H), 1.32–1.83 (m, 5H), 1.23–1.27 (m, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 209.75, 179.35, 144.06, 131.49, 129.22, 125.44, 121.46, 110.04, 74.50, 58.01, 42.11, 34.02, 27.27, 25.09, 24.66; HR-MALDI-MS (DHB): *m*/*z* $[M+Na]^+$ calcd for $C_{14}H_{15}NNaO_3^+$: 268.09441; Found: 268.09464.

Table 10. Aldol reaction of isatin with cyclohexanone.

Catalyst	Yield [%]	*syn*:*anti*/*de*	*ee anti* [%]	*ee syn* [%]
58a	51	60:40/20	0	0
58b	48	55:45/10	6	7(3*S*, 1*R*')
58c	50	80:20/60	4	7(3*R*,1'*S*)
58d	60	97:3/94	25	36(3*R*,1'*S*)
58e	46	89:11/78	49	62(3*R*,1'*S*)
58f	48	83:17/66	45	71(3*R*,1'*S*)
58h	45	69:31/38	2	4(3*R*,1'*S*)

10. Results and discussion

10.1 Development of α-amino acid- and imidazole-derived compounds in the group

Recently, several imidazole derivatives **1**–**10** linked to an α-amino residue were developed in our working group (*Figure 21*).[12–20] These compounds were inspired by the molecule of naturally occurring essential amino acid histidine or its decarboxylation product - histamine. Derivatives **1**–**10** were more or less successfully applied as optically active nitrogen ligands in various asymmetric reactions, ionic liquids, imidazoliophanes and biologically active compounds.

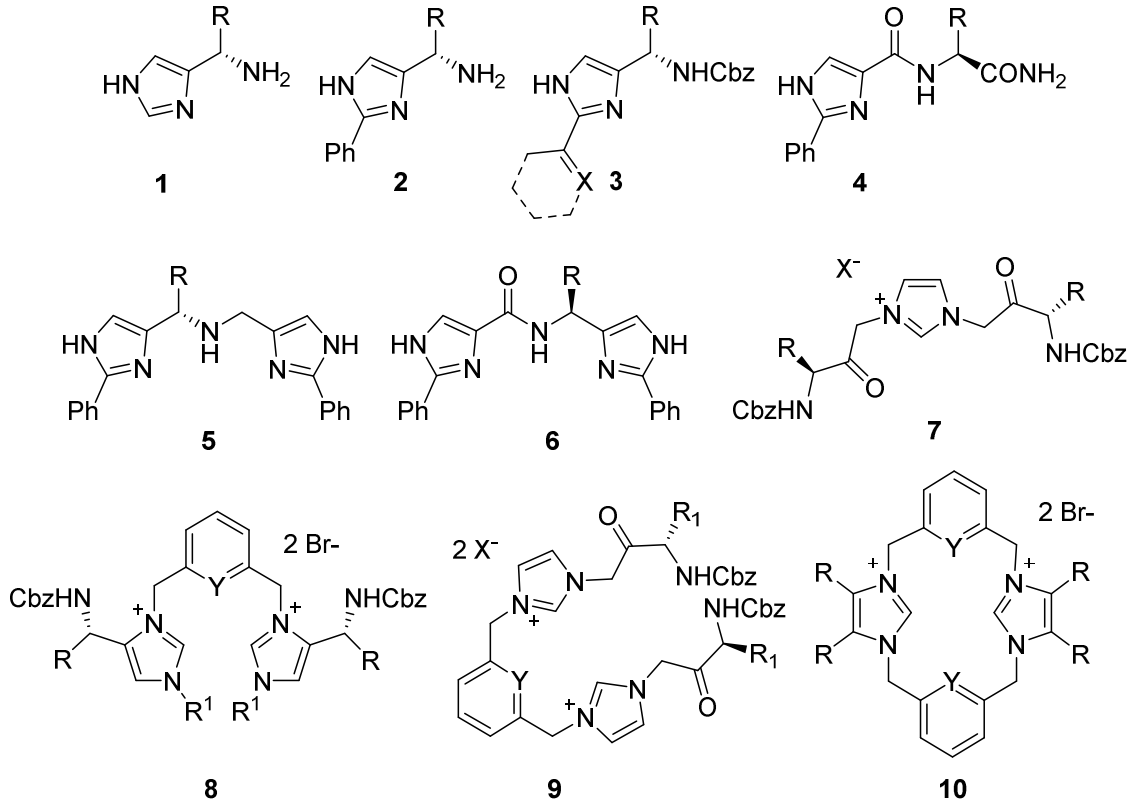
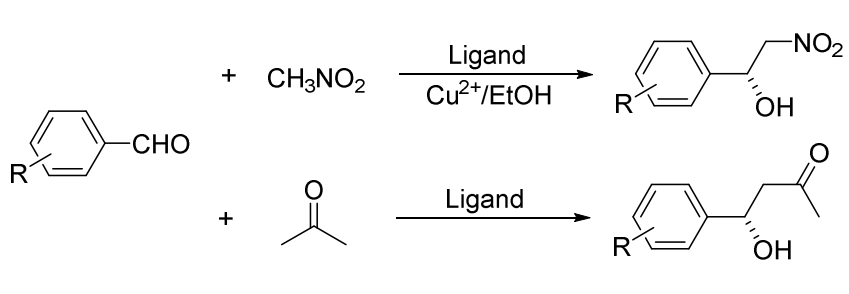


Figure 21. *Imidazole derivatives linked to an α-amino residue.*

Whereas in derivatives **1**–**3** is the α-amino acid an integral part of the imidazole ring, 2-phenylimidazole in derivative **4** has been linked to α-amino acid *via* amidic bond. Parent molecules **1**–**2** are accessible from CBz-protected α-amino acids, their activation *via* mixed anhydrides, reaction with diazomethane to α-diazoketones and subsequent transformation to α-bromoketones. These were finally condensed with amidines.[12–13] Additional heteroaromatic moieties in derivatives **3** can be introduced via Negishi cross-coupling reaction.[14] On the contrary, the synthesis of **4** is as simple as reaction of 2-phenylimidazole-4-

carboxylic acid with various α-amino acid amides.[15] Subsequently, biimidazoles **5** have been proposed and synthesized as novel tridentate ligands. The synthesis starts from the previously prepared chiral amines **2** that were condensed with (hetero)aromatic aldehydes (mostly 2-phenylimidazole-4-carbaldehyde).[16] A similar condensation of amines **2** with 2-phenylimidazole-4-carboxylic acid led to analogous derivatives **6**.[17] Chiral amines **2** and **4** as well as tridentate ligands **5** and **6** have been applied as nitrogen ligands in copper(II)-catalyzed nitroaldol (Henry reaction) and aldol condensation (*Figure 22*). As can be seen, the performance of these ligands/organocatalysts in both reactions is modest. Whereas these compounds provided the desired (nitro)aldol in relatively good chemical yields, the attained enantiomeric excesses hardly exceeded 30 % in the Henry reaction, stereochemical application of **4** in the aldol condensation failed at all.



Ligand	ee [%]
2	3 - 28
4	2 - 13
5	13 - 32
6	5 - 19

Ligand	ee [%]
4	3 - 6

Figure 22. *Screening of ligands* ***2-6*** *in asymmetric Henry and aldol reactions.*

On imidazole, the α-amino residue can also be attached on nitrogen atoms as demonstrated by imidazolium derivatives **7**. This concept has further been extended by bridging two imidazole derivatives bearing α-amino acid residue at C4 to afford dicationic compounds **8** and **9**.[18] Hence, whereas derivatives **7** can be considered as optically active ionic liquids, dicationic **8** and **9** are open form of imidazoliophanes as shown for example on **10**. In the aforementioned derivatives **1**–**10**, the α-amino acid residues are always connected at imidazole N1/N3/C4 positions with the (protected) primary amino group present at the stereogenic center. According to the current state-of-the-art, various primary amines have been successfully applied as organocatalysts in various asymmetric reactions.[47–53] Very often, their parent backbone is derived from α-amino acid as suitable and readily available source of chirality.[54–56] Based on this, my synthetic attempts were focused on development of new chiral benzo[*d*]imidazole derivatives **58** bearing various essential α-amino acid residues appended at the C2 (*Figure 23*) and their applications as organocatalysts in selected asymmetric reactions.

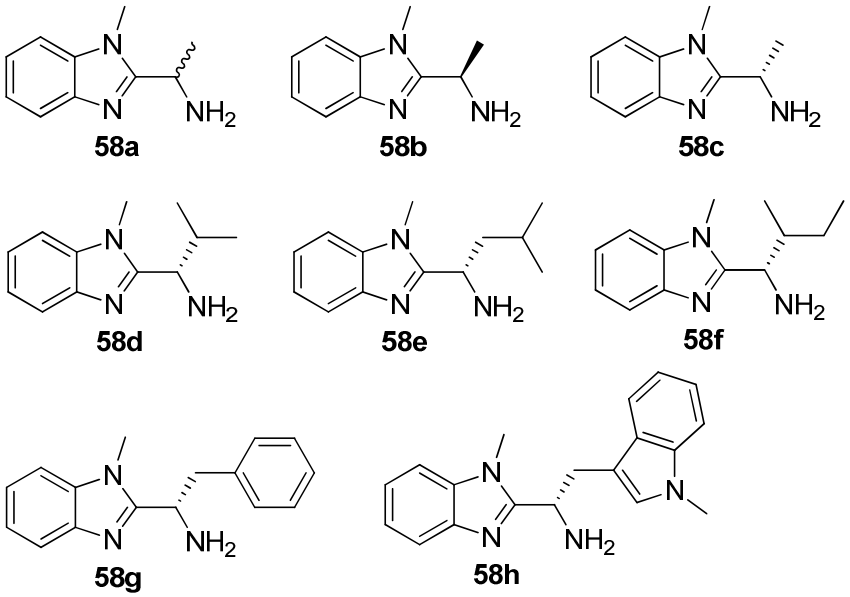
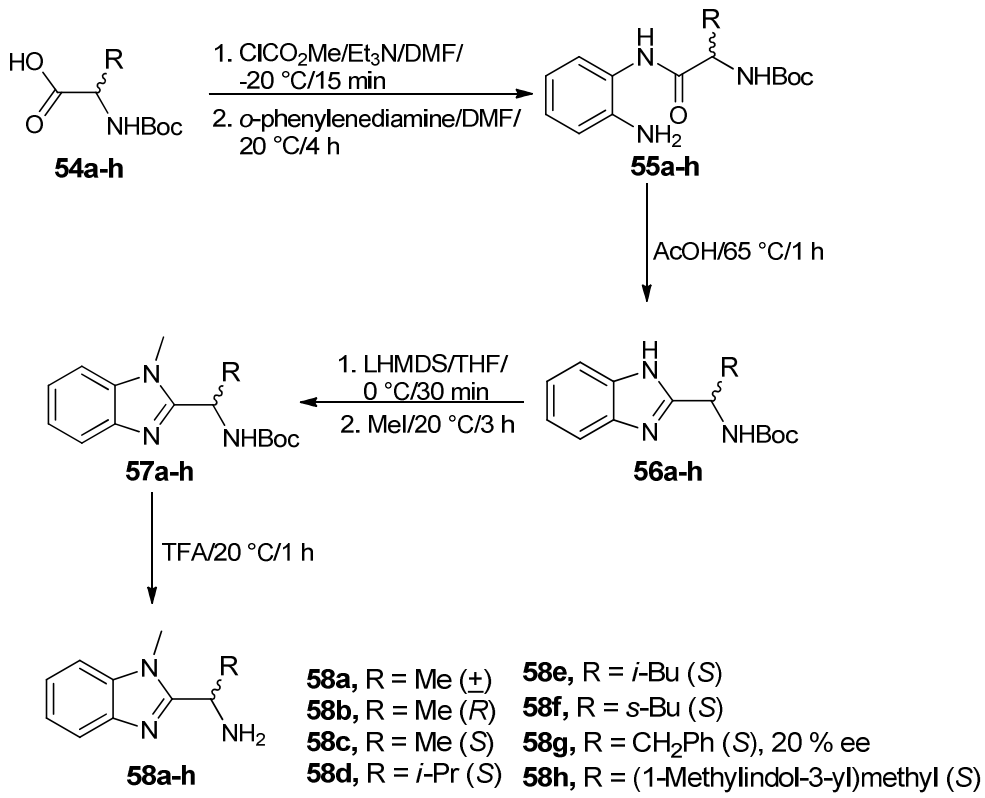


Figure 23. S*tructure of target α-amino acid and benzo[d]imidazole derived primary amines* ***58a–h****.*

10.2 Synthesis of target benzo[*d*]imidazoles

The synthesis of benzo[*d*]imidazole derived primary amines **58a–h** have been carried out via the reaction path shown in *Scheme 34*. The commercially available Boc-protected (±)-alanine, (*S*)-alanine, (*R*)-alanine, (*S*)-valine, (*S*)-leucine, (*S*)-isoleucine, (*S*)-Phenylalanine, and (*S*)-1-methyl tryptophan (**54a–h**) were used as starting materials.



Scheme 34. *Synthesis of primary amine **58a-h**.*

These Boc-protected α-amino acids **54a–h** were activated via mixed anhydride (ClCOOMe/Et_3N/DMF) and subsequently treated with *o*-phenylenediamine to afford amino-amides **55a–h** with the yields ranging from 71 to 84 %. A direct reaction between α-amino acids **54a–h** and *o*-phenylenediamine has also been examined but proved very difficult and low yielding. Therefore, it was necessary to activate the carboxylic group to mixed anhydride by the reaction with alkylchloroformate at low temperature. Subsequent reaction with *o*-phenylenediamine afforded smoothly amino-amides **55a–h** that were used directly in the next reaction step – cyclization to benzo[*d*]imidazoles **56a–h**. The reaction has been accomplished by simple heating of **55a–h** in acetic acid. Subsequent *N*-alkylation was performed to avoid benzo[*d*]imidazole tautomerism. Thus, benzo[*d*]imidazole derivatives **56a–h** were treated with lithium bis(trimethylsilyl)amide (LHMDS) and iodomethane to provide *N*-methyl derivatives **57a–h** with the 50-86% isolated yields. In contrast

to products **57a**–**f** and **57h**, a partial racemization of phenylalanine derivative **57g** was observed within this step (52 % *ee*). Unfortunately, all other attempted *N*-alkylation systems including milder bases such TEA or Na_2CO_3 were unsuccessful as well.[57] Moreover, Boc group removal on **57g** has been accompanied by a further racemization and **58g** was obtained with only 20 % *ee*. On the contrary, all remaining target amines **58a–f** and **h** were gained by Boc group removal using trifluoroacetic acid (TFA) without any racemization. Acid mediated cleavage of the *tert*-butoxycarbonyl group is an established procedure for deprotecting *N*H-Boc amines and proceeds in three steps.[58] The carbamate is first protonated at the most basic oxygen to produce carboxonium ion, then heterolytic *O*-*t*butyl bond cleavage yielding neutral carbamic acid takes place followed by final decomposition to amine. It should also be noted here, that CBz-protected α-amino acids undergo similar reaction transformation except the final CBz group removal that proved very difficult. All attempts to CBz group removal from Alanine benzo[*d*]imidazole derivative similar to **58c** under various conditions failed at all. The complete reaction sequence is outlined in *Scheme 34* and resembles that used to generate BocGly derivative described by Lazarus et al.[59] *Table 11* shows starting α-amino acids, absolute configurations, and yields of all intermediates and final products.

Table 11. Structure, absolute configurations, and yields of primary amines **58a–h** and intermediates **55a–h** to **57a–h**.

α-amino acid	R	Configuration	Yield [%]			
			55a–h	**56a–h**	**57a–h**	**58a–h**
(±)-Ala	Me	±	76	78	86	45
(*R*)-Ala	Me	*R*	78	82	76	48
(*S*)-Ala	Me	*S*	76	75	66	45
(*S*)-Val	*i*-Pr	*S*	82	71	58	61
(*S*)-Leu	*i*-Bu	*S*	71	66	65	39
(*S*)-Ile	*s*-Bu	*S*	80	76	64	36
(*S*)-Phe	Ph	*S*	74	79	50	38
(*S*)-1-MeTrp	Metrp	*S*	84	64	64	53

10.3 Spectral properties

All of the synthesized benzo[*d*]imidazoles were characterized by $^{1}H/^{13}C$-NMR spectroscopy and HR-MALDI-MS (DHB) analysis. As an example, the ^{1}H-NMR spectra of Alanine derivatives **58a**–**c** showed doublet of the $CH(NH_2)C\mathit{H}_3$ group, singlet of N-$C\mathit{H}_3$ group, quartet of $C\mathit{H}NH_2$ group and pattern in aromatic part corresponding to the fused benzene ring, see *Figure 24*.

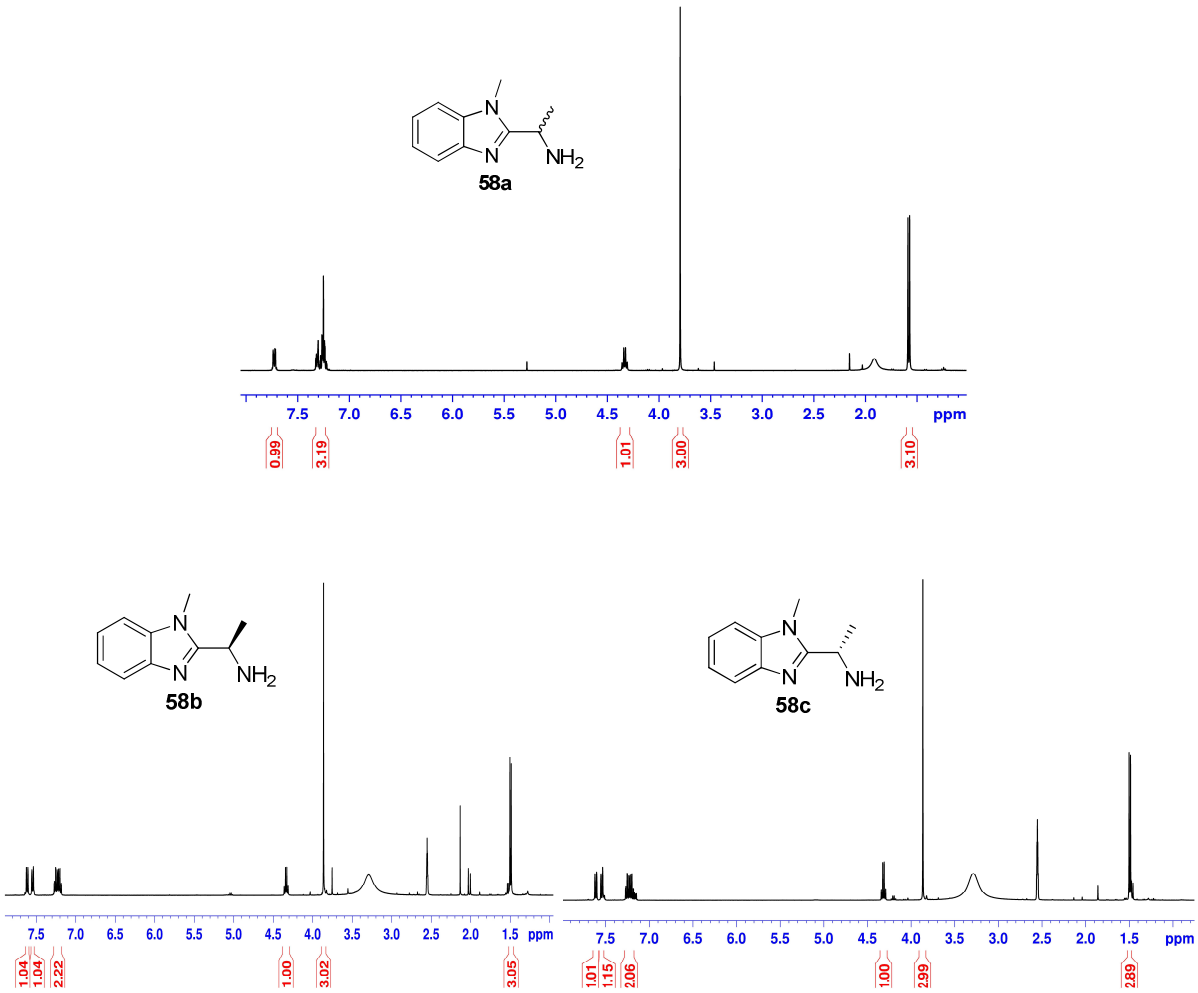


Figure 24. *^{1}H NMR spectrum of racemic **58a** ($CDCl_3$, 400 MHz) as well as pure enantiomers **58b** and **58c** (DMSO-d_6, 400 MHz).*

To verify optical purity of target amines **58b** and **58c**, these were measured with chiral derivatizing agent (CDA) and compared to the similar spectra of racemate **58a**. Mosher's acid ((*R*)-methoxy(trifluoromethyl)phenylacetic acid) seems to be well-suited CDA in this respect. This compound, introduced by H. Mosher in 1969, is considered as reliable and effective chiral shift reagent for analyzing and determining optical purity of primary amines.[60] The ^{1}H-NMR spectra of **58a**–**c** measured with (*R*)-Mosher's acid are shown in *Figure 25*. As can be seen, the racemate **58a** showed two set of signals as a result of formation of both diastereoisomers, while the pure enantiomers **58b**–**c** showed only one set of signals. This is obvious especially by comparing aliphatic parts of the spectra. Clear differences in the chemical shifts of protons located near the molecule's stereocenter are distinguishable (doublets and quartet for $CH(NH_2)C\mathit{H}_3$ and $C\mathit{H}NH_2$ groups, respectively). Hence, this implies that no racemization takes place throughout the entire reaction sequence. NMR analyses of all remaining target amines are shown in the supplement.

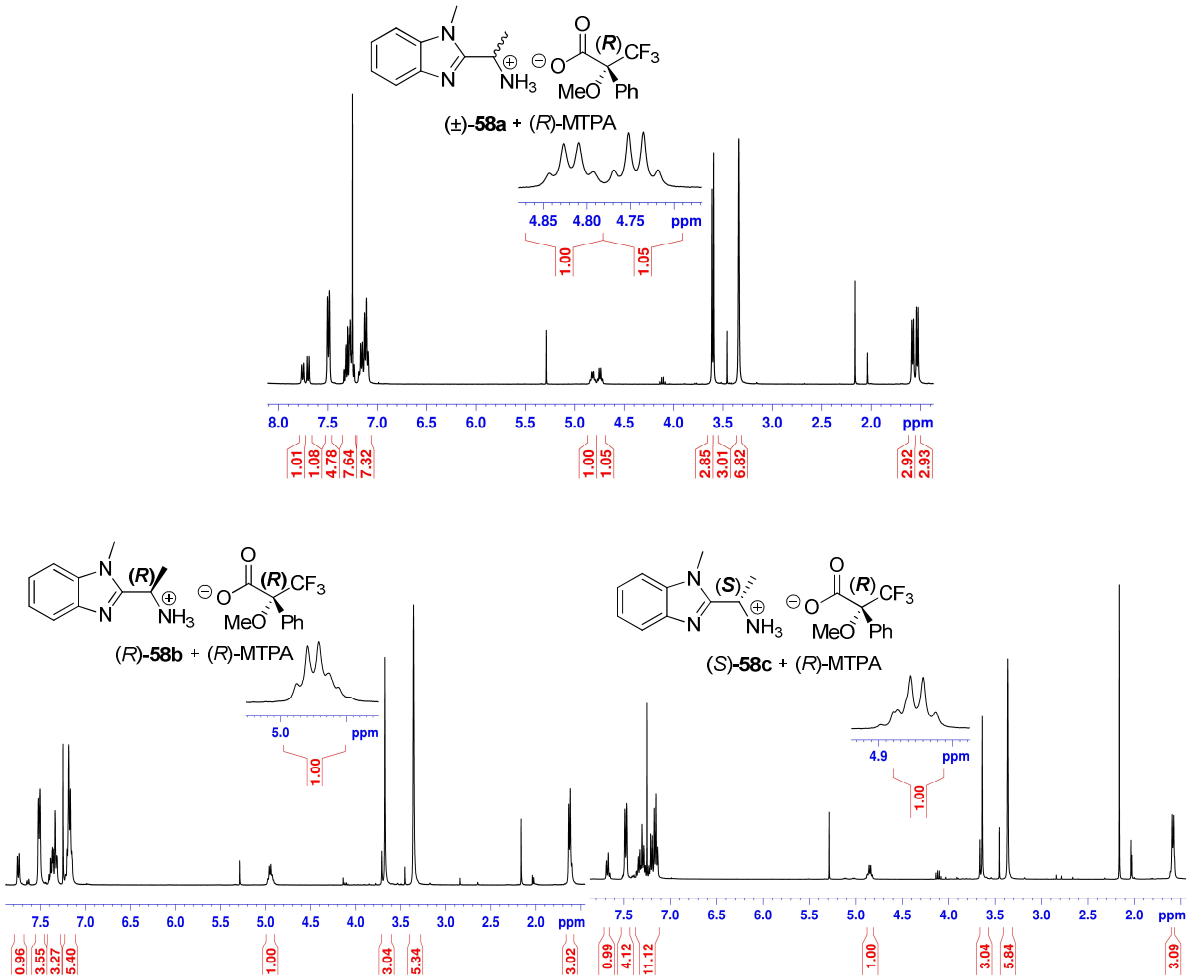


Figure 25. *^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compounds **58a–c** measured with Mosher's acid.*

Optical purity of all target amines **58a–h** has also been checked by employing chiral phase HPLC analysis. For Alanine derivatives **58a–c**, the HPLC diagrams are shown in *Figure 26*. Based on these analyses, the enantiomeric excesses of **58a–c** were estimated to 0, 95, and 99 %, respectively. Moreover, HPLC with chiral stationary phase also allowed to determine the optical purity of "problematic" Phenylalanine derivative **58g**. As can be seen from the enclosed HPLC diagram, this target amine possesses only 20% *ee* (*Figure 26*). HPLC diagrams of all remaining target amines are shown in the supplement.

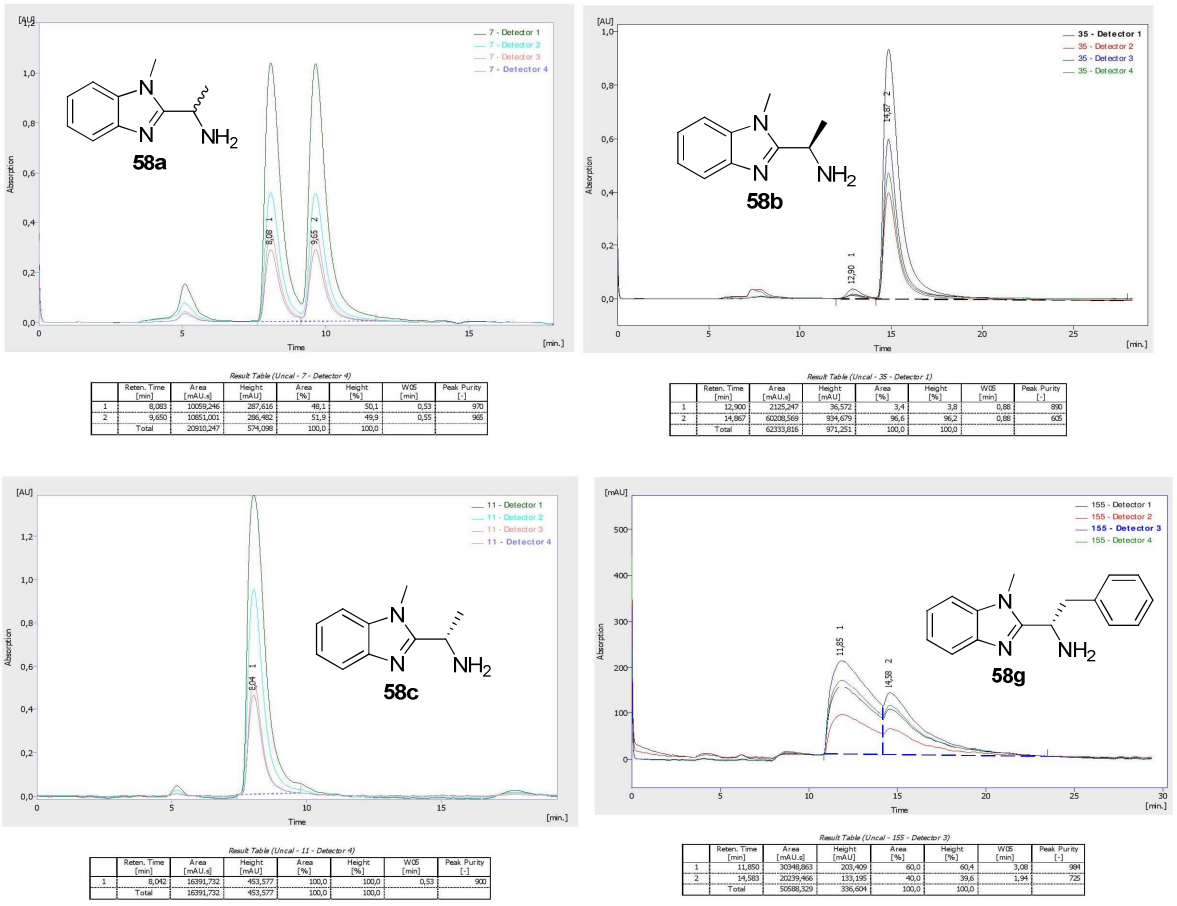


Figure 26. *Chiral phase HPLC analyses of catalyst* ***58a–c*** *and* ***58g****.*

Structure and purity of all target compounds and intermediates were also analyzed by HR-MALDI-MS. The experimental and calculated HR-MALDI-MS (DHB) spectrum of **58f** is shown in *Figure 27*, remaining ones are shown in the supplement. As a general trend, all target amines except Tryptophan derivative **58h** showed both expected $[M+H]^+$ and $[M+Na]^+$ ions. The experimental *m/z* values for **58f** were found 218.16473 and 240.14718 Da. These values correlate well with the calculated masses of 218.16517 and 240.14712 Da within the limit of 4 ppm ($\Delta m/z$ = 2.5 and 0.2 ppm, respectively).

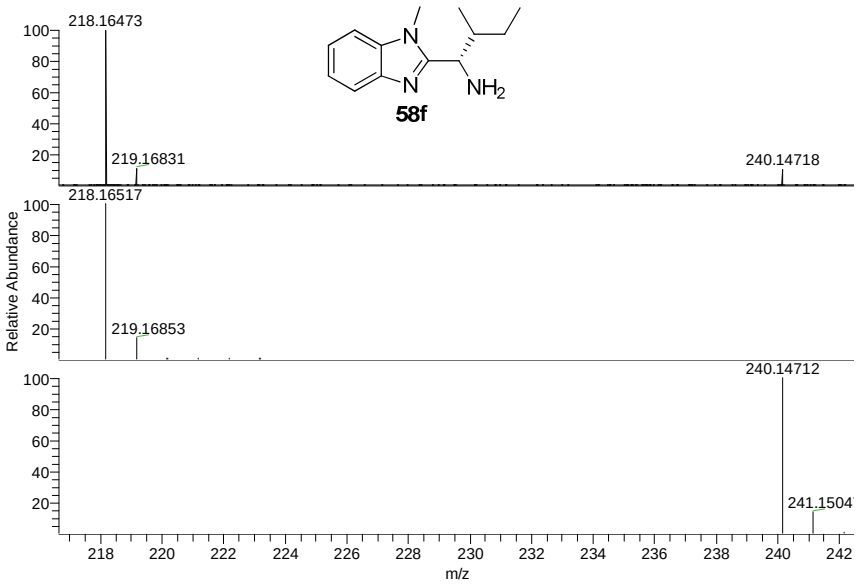


Figure 27. *Experimental (up) and calculated HR-MALDI-MS spectra (DHB) of* ***58f****.*

10.4 Amines 58a-h as optically active organocatalysts

Carbon-carbon bond forming reactions represent undoubtedly the most desired and used synthetic tool of organic chemists. Among such reactions, a process accompanied by the formation of a new stereogenic center is of high interest. Aldol reaction providing general access to β-hydroxycarbonyl compounds represents such a case.[61] Based on the aforementioned literature search, Vincent *et al*. showed application of 5,6-dimethylbenzo[*d*]imidazole **44** (*Figure 28*) linked to L-proline residue in asymmetric aldol reaction (*Scheme 23*).[37] This new chiral benzimidazole-pyrrolidine **44** (BIP) was able to organocatalyze aldol process between the acetone and 4-nitrobenzaldehyde in the presence of an Brönsted acid, leading to the aldol adduct in high yield and enantioselectivity.

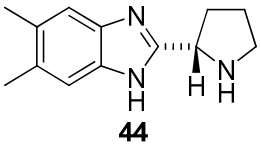
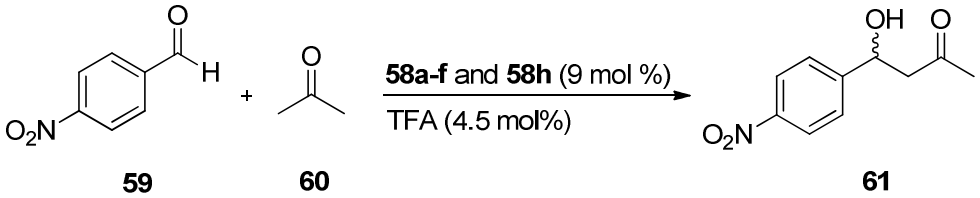


Figure 28. *The most successful organocatalyst – BIP.*

Hence, all prepared optically pure primary amines **58a**–**h** except **58g** bearing α-amino acid and benzo[*d*]imidazole pendants (*Figure 23*) were investigated as organocatalyst in aldol reaction of 4-nitrobenzaldehyde and isatin with acetone and cyclohexanone. The initial screening has been carried out in an acid-catalyzed reaction utilizing 4-nitrobenzaldehyde acceptor and acetone donor. The reaction conditions and the achieved results are summarized

in *Scheme 35* and *Table 12*. After initial elaboration, all reactions were carried out on 1 mmol scale with 9 mol% of the catalyst and the reaction time/temperature of 24 h/20 °C. According to the observations on benzoimidazole-pyrrolidine (BIP) ligand made by Vincent *et al.*,[37] we have used TFA (4.5 mol%) as a proton source.



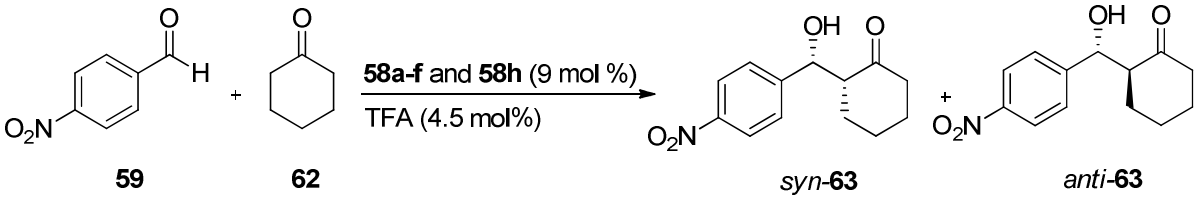
Scheme 35. *Asymmetric aldol reaction of 4-nitrobenzaldehyde with acetone.*

Table 12. Results of the aldol reaction of 4-nitrobenzaldehyde with acetone.

Catalyst	Yield [%]	*ee* [%]	Configuration
58a	51	0	±
58b	40	32	*S*
58c	46	32	*R*
58d	48	49	*R*
58e	51	59	*R*
58f	59	65	*R*
58h	51	3	*R*

Such standard condition allowed investigation of the structure-catalytic activity of the synthesized amines **58a–f** and **58h**. Aldol products **61** were isolated by column chromatography and the enantiomeric excesses were determined by HPLC. The reaction catalyzed by racemic alanine-derived amine (±)-**58a** afforded aldol product **61** in the yield of 51 % and with anticipated 0 % *ee* (*Table 12*). Corresponding catalysts (*R*)-**58b** and (*S*)-**58c** afforded aldols **61** in the yields of 40/46 % and modest optical purities 32/32 % *ee* (*Table 12*). In general, all organocatalysts having (*S*)-configuration provided (*R*)-aldol while amine (*R*)-**58b** provided opposite (*S*)-enantiomer **61**. This is in agreement with that observed by Vincent *et al.*[37] More interestingly, attained enantiomeric excesses increased with increasing bulkiness of the R-substituent. The highest *ee* values of 59 and 65 % were gained for the aldol reaction catalyzed with leucine- and isoleucine-derived amines (*S*)-**58e** and (*S*)-**58f** bearing *iso*- and *sec*-butyl R-substituents (*Table 12*). Thus, the stereochemical outcome of the aldol reaction can significantly be tuned by alternation of the α-amino acid pendant appended to benzimidazole C2. On the contrary, attaching heterocyclic (indol) moiety as in tryptophan-derived catalyst **58h** reduced the stereochemical outcome of the aldol process very significantly to 3 % *ee* (*Table 12*).

The catalytic activity of primary amines **58a–f** and **58h** has further been evaluated in the aldol process performed on cyclohexanone (*Scheme 36*). All reactions were conducted with 4-nitrobenzaldehyde (1.0 mmol) and cyclohexanone (7.5 mL) in the presence of the primary amines **58a–f** and **58h** (0.09 mmol) and the TFA (3.5 L, 0.045 mmol) at 25 °C for 72 h.



Scheme 36. *Asymmetric aldol reaction of 4-nitrobenzaldehyde with cyclohexanone.*

Table 13. Aldol reaction of 4-nitrobenzaldehyde with cyclohexanone.

Catalyst	Yield [%]	*syn*:*anti*/*de*	*ee syn* [%]	*ee anti* [%]
58a	48	2:98/96	0	0
58b	46	3:97/94	32 (2*S*,1'*S*)	29(2*R*,1'*S*)
58c	49	17:83/66	23(2*R*,1'*R*)	32(2*S*,1'*R*)
58d	51	7:93/86	32(2*R*,1'*R*)	62(2*S*,1'*R*)
58e	60	4:96/92	23(2*R*,1'*R*)	32(2*S*,1'*R*)
58f	64	8:92/84	31(2*R*,1'*R*)	39(2*S*,1'*R*)
58h	49	12:88/76	10(2*R*,1'*R*)	36(2*S*,1'*R*)

The reaction outcomes are summarized in *Table 13*. The isolated chemical yields range from 46 to 64 % and slightly increase with the extension of the R-substituent. The aldol process with cyclohexanone afforded aldol **63** as a set of *syn* and *anti* diastereomers. The *anti*-diastereoisomer **63** was dominantly isolated regardless on the structure of the catalyst used. The attained *syn*/*anti* ratios and respective *de* for optically pure organocatalysts **58a–f** and **58h** varied from 2:98 to 12:88 respective 94 to 66 %. The aldol reaction catalyzed by alanine-derived amines (±)-**58a**, (*R*)-**58b**, and (*S*)-**58c**, afforded 0/0, 32/29, and 23/32 % *ee*s for *syn*/*anti* diastereoisomers, respectively. The absolute configurations of the obtained aldols depend on the configuration of the used catalysts (e.g. **58b** vs. **58c**). Whereas the attained *ee* for the *syn*-stereoisomers are modest (23-32 %), the *ee* values for the dominant *anti*-stereoisomers range from 29 to 62 %. By using (*S*)-catalysts **58c–f** and **58h**, (2*S*,1'*R*) and (2*R*,1'*R*) *anti*/*syn* enantiomers were isolated. The highest enantiomeric excess 62 and 39 % have been achieved within the aldol reaction catalyzed

by valine- and isoleucine-derived amines (*S*)-**58d** and (*S*)-**58f**. Hence, branching of the R-substituent on the carbon atom next to the stereogenic center of amines **58a–f** and **58h** seems to be crucial for asymmetric induction. The *anti*/*syn* ratios were determined by ^{1}H NMR spectra and chiral phase HPLC analysis. Both these analyses revealed *anti* relative configuration of the major diastereoisomer. The absolute configuration of the major *anti* diastereoisomer was assigned as 2*S*,1'*R* by comparing the HPLC retention times of its two enantiomers with the reported values.[45] Whereas *anti*-diastereoisomers possess configurations (2*S*,1'*R*) and (2*R*,1'*R*) and were obtained by employing (*S*)-catalysts **58c–f** and **58h**, the aldol reaction catalyzed by (*R*)-catalyst **58b** afforded diastereoisomers with *syn* relative configurations (2*S*,1'*S*) and (2*R*,1'*S*). ^{1}H NMR analysis has also been employed to determine the *syn*/*anti* ratio of the particular diastereoisomers as can be seen from *Figure 29*.

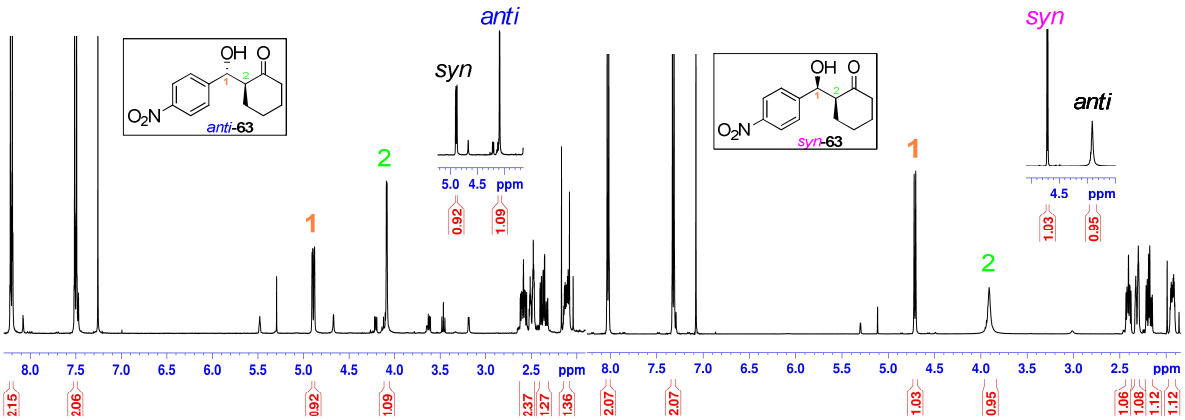
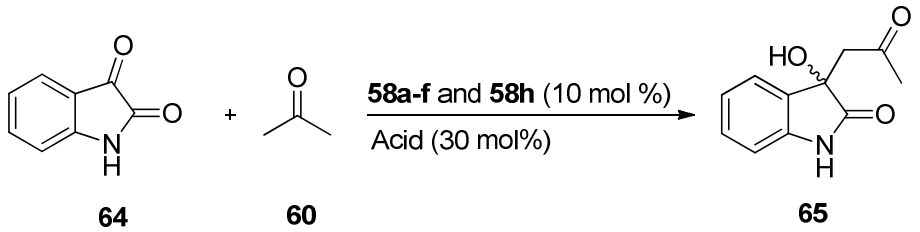


Figure 29. *An example of the ^{1}H NMR spectra ($CDCl_3$, 400 MHz) of diastereoisomer **63** obtained by employing (S)- or (R)-catalysts used for anti/syn ratio determination.*

Organocatalyzed aldol reactions have also been utilized for the construction of miscellaneous organic substances such as natural products (epothilone), pharmaceuticals (atorvastatin, erythromycin, steroids), explosives (pentaerythritol tetranitrate), α,β-unsaturated carbonyl compounds (reactive substrates), etc. Among these and many others, 3-hydroxy-2-oxindole is one of the key structural units found in a large variety of natural products and drug candidates, having wide spectrum of biological activities.[62] Especially 3-alkyl-3-hydroxy-2-oxindole structural motive is of great importance for medicinal chemistry. It can be found in many drugs and natural products such as TMC-95A-D,[63] donaxaridine,[64] convolutamydines,[64] dioxibrassinine,[65] and 3′-hydroxyglucoisatisi.[66] These molecules display diverse biological and pharmacological activities such as potent antioxidant, anticonvulsant, anticancer, anti-HIV, and neuroprotective properties. The most

straightforward synthetic approach towards 3-substituted-3-hydroxy-2-oxindoles is via nucleophilic addition to isatin (aldol process).
In 2005, Tomasini et al. reported a first enantioselective aldol reaction of isatin with acetone using 10 % of dipeptide containing secondary amine at the N-terminus.[67] Primary amines as well as carbohydrate-derived alcohols were successfully screened as organocatalysts in enantioselective aldol process between cyclohexanone/acetophenone and isatins.[68,69] Especially primary amines turned out to efficiently catalyze aldol process of isatin derivatives[70-74] and, therefore, we focused our further attention to utilize amines **58a–f** and **58h** in asymmetric aldol reaction affording 3-substituted-3-hydroxyindolin-2-ones in a single operational method. Hence, beside application of **58a–f** and **58h** as organocatalyst in aldol reaction with 4-nitrobenzaldehyde, we next focused on their catalytic performance in the direct aldol reaction on isatin. In initial optimization attempts, a model reaction was carried out between isatin and acetone using 10 mol % of the catalysts **58a–f** and **58h** (*Scheme 37 and Table 14*).



Scheme 37. *Asymmetric aldol reaction of isatin with acetone.*

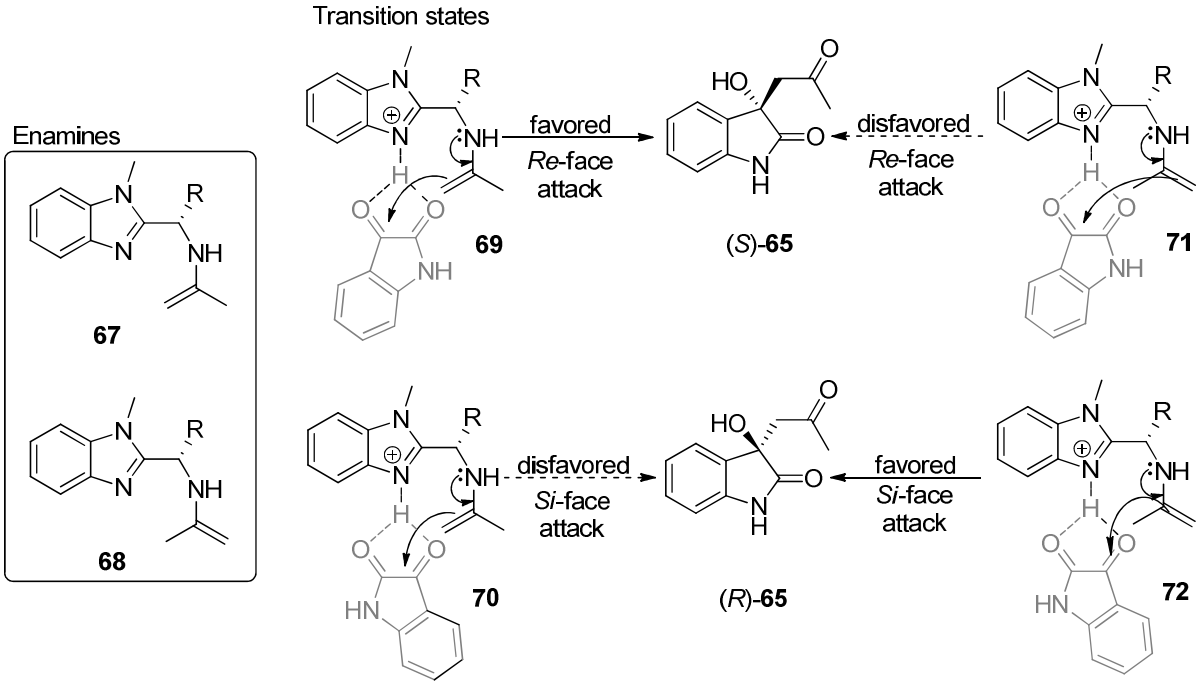
Table 14. Aldol reaction of isatin with acetone.

Catalyst	Acid	Yield [%]	*ee* [%]	Configuration
58a	$PhCO_2H$	56	0	±
58b	TFA	58	1	*R*
58b	AcOH	64	2	*R*
58b	$PhCO_2H$	65	4	*R*
58c	TFA	64	1	*S*
58c	AcOH	66	2	*S*
58c	$PhCO_2H$	68	4	*S*
58d	TFA	57	3	*S*
58d	AcOH	59	5	*S*
58d	$PhCO_2H$	67	6	*S*
58e	TFA	62	12	*S*
58e	AcOH	64	15	*S*
58e	$PhCO_2H$	74	16	*S*
58f	TFA	67	18	*S*
58f	AcOH	72	22	*S*
58f	$PhCO_2H$	70	24	*S*
58h	TFA	61	1	*S*
58h	AcOH	62	1	*S*

58h	$PhCO_2H$	66	3	*S*

It has been well documented that additives may improve the catalytic efficiency by fast enamine formation.[75] According to literature, we have examined TFA, acetic and benzoic acids as proton sources (30 mol %).[47] As can be seen from the data gathered in *Table 14*, benzoic acid showed the best catalytic efficiency (attained chemical yields and enantioselectivities) as compared to other two acids. Under these conditions, the aldol process between isatin and acetone utilizing **58a**–**f** and **58h**/$PhCO_2H$ system afforded product **65** with the yields of 56–74 % and 3-24 % *ee* (*Table 14*). A clear trend in increasing enantioselectivities from 4 to 24 % *ee* (*Table 14*, catalyst **58b**→**58c**→**58d**→**58e**→**58f**) can be seen within a series of amines with aliphatic residues **58a**–**f**. This is in accordance with the observation made for the aldol reaction with 4-nitrobenzaldehyde **59** (*Table 12*). The highest chemical yields (74 and 70 %) and enantioselectivities (16 and 24 %) were obtained for the most sterically hindered catalysts **58e** and **58f** derived from leucine and isoleucine (*Table 14*). Similarly to the aldol reaction with 4-nitrobenzaldehyde **59** (*Table 12*), the amine **58h** bearing tryptophan pendant showed very low catalytic performance.

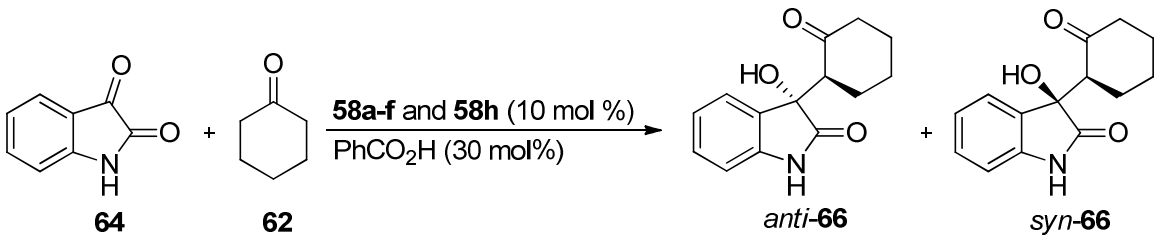
Based on our observations and the absolute configuration of obtained aldol **65**, a plausible catalytic model for the reaction of acetone and isatin was proposed (*Scheme 38*).



Scheme 38. *Structure of both enamine **67** and **68** and proposed transition states **69–70** for the aldol reaction between 64 and 60 catalysed by benzo[d]imidazole-derived primary amines **58a–h**.*

As a first step, the amines **58a**–**f** and **58h** react with **60**/**62** to form an enamine intermediate. In principle and according to a recent mechanistic investigation of Kočovský et al.,[46] both *syn*- and *anti*-rotamers **67** and **68** can be envisaged. Whereas the *anti*-enamine **68** is kinetically favored, the *syn*-enamine **67** is thermodynamically more stable and, under equilibrium condition, the subsequent aldol process will proceed mainly via **67**. A two principal roles of the co-catalyst (acid) can be envisaged: i) it accelerates formation of enamines **67** and **68** and ii) it also protonates the nitrogen atom of the benzimidazole backbone to form benzimidazolium salt. Benzimidazolium ion is most likely hydrogen bonded to carbonyl groups of **64**, which influences their reactivity and also brings reacting species close together for the cross aldol reaction. The transition states for both enamines **67** and **68** shown in Scheme 2 suggest easiest access of **67** to attack **64** *via Re*-face (transition state **69**), which leads to formation of (*S*)-**65**. On the contrary, enamine **68** would also attack **64** via *Si*-face (transition state **72**) leading to (*R*)-**65**. Both these concurrent attacks are reflected by low enantioselectivities obtained in the aldol reaction between acetone and **64** (*Table **14***, maximal 24% *ee*). On the contrary, the reaction with cyclohexanone (*Table **15***) afforded **66** with *ee* up to 71 %. Whereas in amines **58a**–**f** are the aliphatic R-substituents involved only as bulky substituent without capability of protonation/coordination, in tryptophan derivative **58h** another transition states involving indolyl residue can be envisaged. This most likely accounts for the low stereochemical performance of this derivative.

The catalytic activity of primary amines **58a–f** and **h** has further been evaluated in the aldol reaction of isatin with cyclohexanone (*Scheme 39*). In contrast to the reactions with acetone, the reaction of isatin with cyclohexanone required prolonged reaction time (96 vs. 108 h). The reaction and the achieved results are summarized in *Scheme 39* and *Table 15*.



Scheme 39. *Asymmetric aldol reaction of isatin with cyclohexanone.*

Table 15. Aldol reaction of isatin with acetone.

Catalyst	Yield [%]	*syn*:*anti*/*de*	*ee anti* [%]	*ee syn* [%]
58a	51	60:40/20	0	0
58b	48	55:45/10	6	7(3*S*, 1*R*')
58c	50	80:20/60	4	7(3*R*,1'*S*)
58d	60	97:3/94	25	36(3*R*,1'*S*)
58e	46	89:11/78	49	62(3*R*,1'*S*)
58f	48	83:17/66	45	71(3*R*,1'*S*)
58h	45	69:31/38	2	4(3*R*,1'*S*)

The aldol products **66** were isolated in the yields of 45 to 60 % as a set of *syn* and *anti* diastereomers (*Table 15*). Alanine-derived amines **58a**–**58c** provided aldol adducts **66** with the yield about 50 % and low diastereo- and enantioselectivities (*Table 15*). Valine, leucine and isoleucine derivatives **58d**–**f** showed significantly improved stereochemical outcomes (*Table 15*). Attained *syn*/*anti* ratios and *de* values for optically pure organocatalysts **58a**–**f** and **58h** varied from 97:3 to 55:45 and 94 to 10 %, respectively. Valine-derived amine **58d** showed the highest diastereoselectivity (94 % *de*), while leucine and isoleucine derivatives **58e** and **58f** afforded *syn*-**66** with the highest enantioselectivities of 62 and 71 % (*Table 15*). The spectral properties of obtained isomers have been compared with those reported in the literature[76] which allowed determining the *syn/anti* ratios. For instance, the aldol process between **64** and **62** catalyzed by (*S*)-**58d** afforded 60% yield and 97/3 *syn*/*anti* ratio of **66** as determined both by ^{1}H NMR and chiral phase HPLC analysis (*Figure 29*).

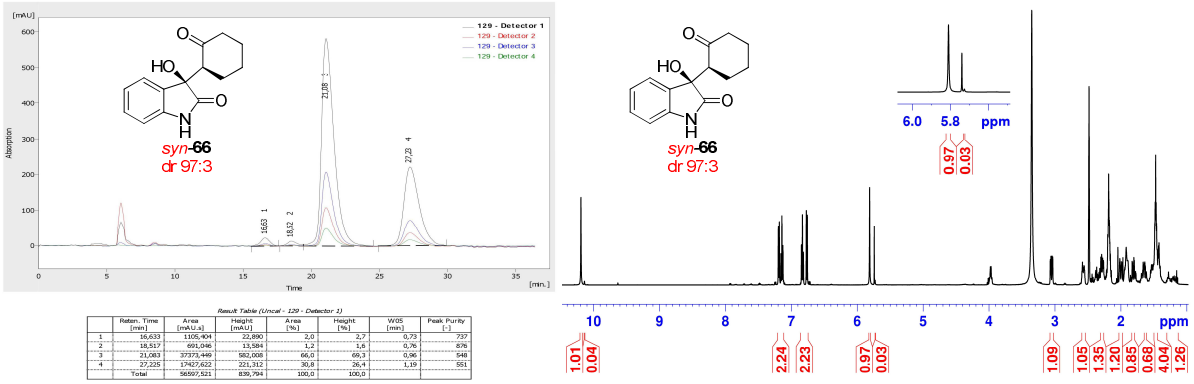


Figure 30. *HPLC analysis and* ^{1}*H NMR (DMSO-*d_6*, 400 MHz) spectrum of aldol* ***66*** *prepared by employing (S)-****58d****.*

11. Conclusion

The performed literature search indicted that compounds bearing chiral α-amino acid residues and heterocyclic moieties, especially benzo[*d*]imidazole and benzo[*d*]oxazole, represent interesting but relatively untapped part of modern organic chemistry. Five general methods leading to benzo[*d*]imidazole derivatives were found, whereas benzo[*d*]oxazoles can be synthesized via four reactions pathways. Recently, these derivatives found first applications in asymmetric synthesis, especially as ligands and organocatalysts, as well as in bio- and pharmachemistry. From the perspective of this dissertation, the main outcome of the literature search is that benzo[*d*]imidazole bearing aliphatic α-amino acid residues may organocatalyze direct (asymmetric) aldol reactions.

A straightforward reaction path towards six new chiral benzo[*d*]imidazole bearing α-amino acid pendants has been developed. Six starting essential α-amino acids were converted to target chiral amines in a four step synthesis. The reaction sequence involves activation of the Boc-amino acid carboxylic acid, reaction with *o*-phenylenediamine and subsequent cyclization to benzo[*d*]imidazole. Subsequent *N*-alkylation avoided benzimidazole tautomerism. Final Boc group removal afforded six new primary amines (*Figure 31*). Alanine derivatives were prepared as a racemic mixture and both optically pure enantiomers. Phenylalanine derivative underwent racemization during the reaction sequence and, therefore, has not further been evaluated. Chemical and optical purities of all target compounds and intermediates were verified by ^{1}H, ^{13}C NMR, HR-MALDI-MS and chiral phase HPLC analysis.

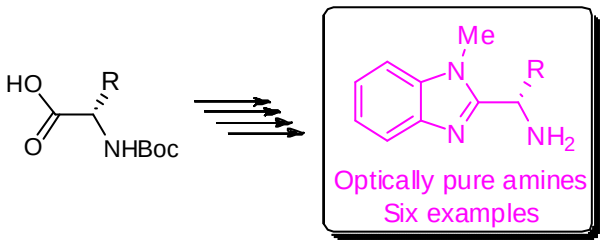


Figure 31. *General approach and structure of six α-amino acid and benzo[d]imidazole derived primary amines* ***58a–h****.*

All prepared amines were investigated as organocatalyst in aldol reaction between 4-nitrobenzaldehyde and isatin acceptors and acetone and cyclohexanone donors. Trifluroacetic and benzoic acids proved to be well suited proton sources for these two reactions organocatalyzed by optically pure primary amines **58a–f** and **58h**. In the aldol reaction of

4-nitrobenzaldehyde with acetone and cyclohexanone, chemical yields of 40–64 % and *ee* and *de* up to 65 and 96 % were achieved. The stereochemical outcomes of the aldol process can be affected by the configuration and bulkiness of the α-amino acid residue. All organocatalysts having (*S*)-configuration provided (*R*)-aldol while amine (*R*)-**58b** provided opposite enantiomer (*S*)-aldol.

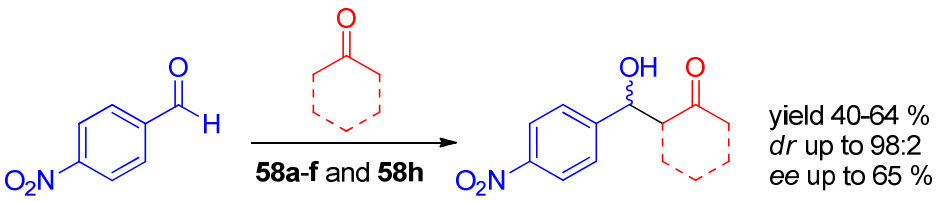


Figure 32. *Aldol reaction of 4-nitrobenzaldehyde with acetone/cyclohexanone.*

The catalytic performance of amines **58a**–**f** and **58h** has also been verified in the direct aldol reaction on isatin. Both acetone as well as cyclohexanone were used as donors. The reaction provided aldol products with both good chemical yields and enantiomeric excesses up to 71 %. The reaction with cyclohexanone provided a set of diastereoisomers with *de* up to 94 %.

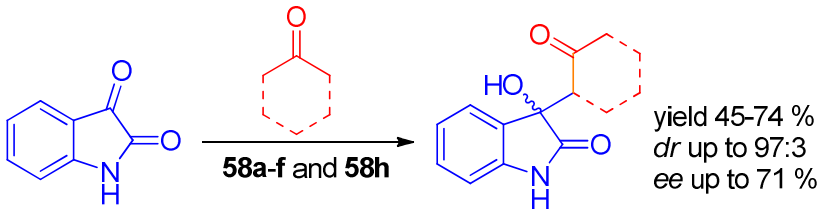


Figure 33. *Aldol reaction of isatin with acetone/cyclohexanone.*

The main outcomes of the research within my dissertation work can be summarized as follows:

1. Based on the literature search, a new class of benzo[*d*]imidazole derivatives bearing α-amino pendants has been designed.
2. Starting from commercially available Boc-protected α-amino acids, a straightforward four-step synthetic path has been developed.
3. Alanine, Valine, Leucine, Isoleucine, Phenylalanine and Tryptophan were successfully utilized as starting materials. Phenylalanine underwent partial racemization.
4. Prepared primary amines proved to be tunable organocatalysts for aldol reactions.
5. Two acceptors and two donors were examined.

6. The absolute configuration of the used organocatalyst predestinates stereochemical configuration of the formed aldol product, while its structure (bulkiness of the R-substituent), significantly affected the asymmetric induction.

The result achieved within this dissertation work were published in the following articles:

1. **Mohite, P. H.**; Drabina, P.; Bureš, F. *Synlett* **2014**, *25*, 491–494.
2. **Mohite, P. H.**; Drabina, P.; Bureš, F. *Synthesis* **2016**, accepted.

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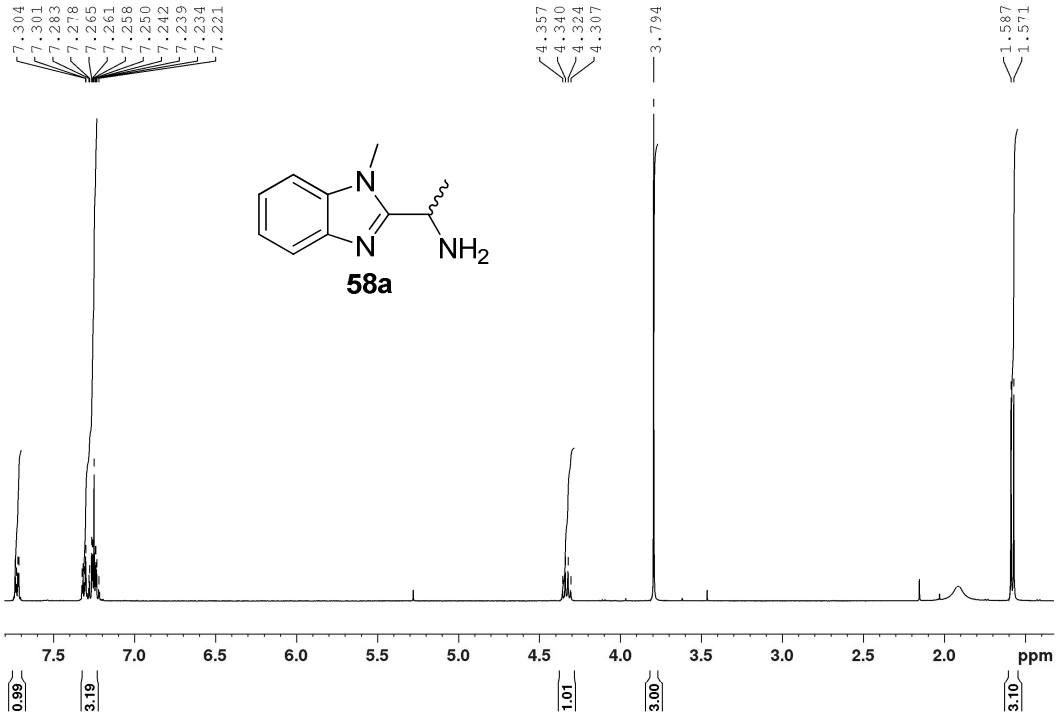
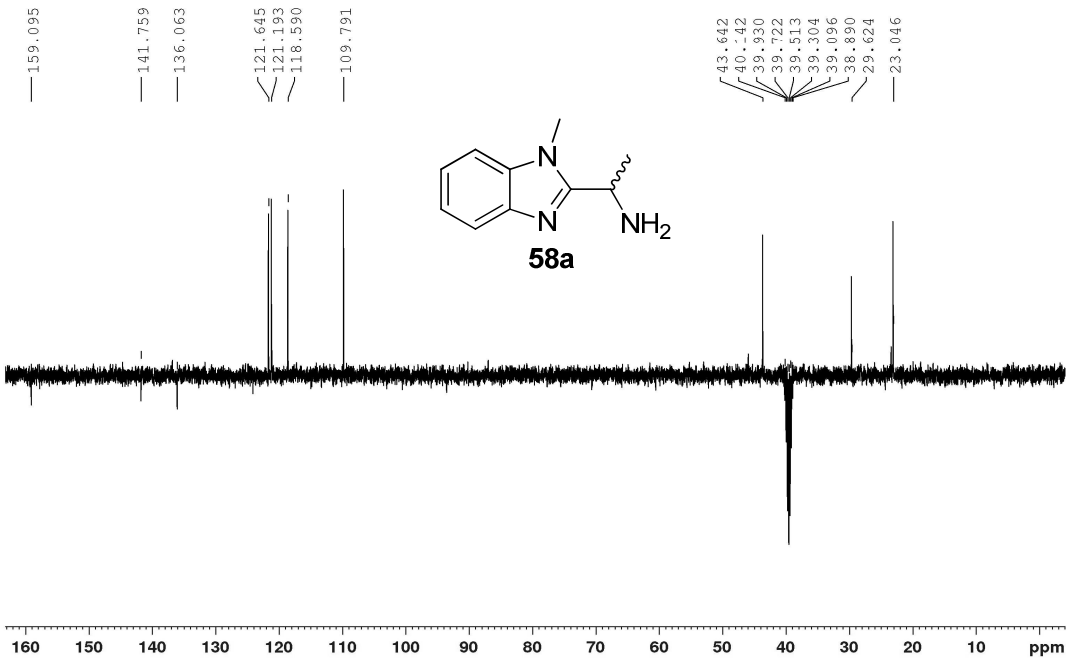
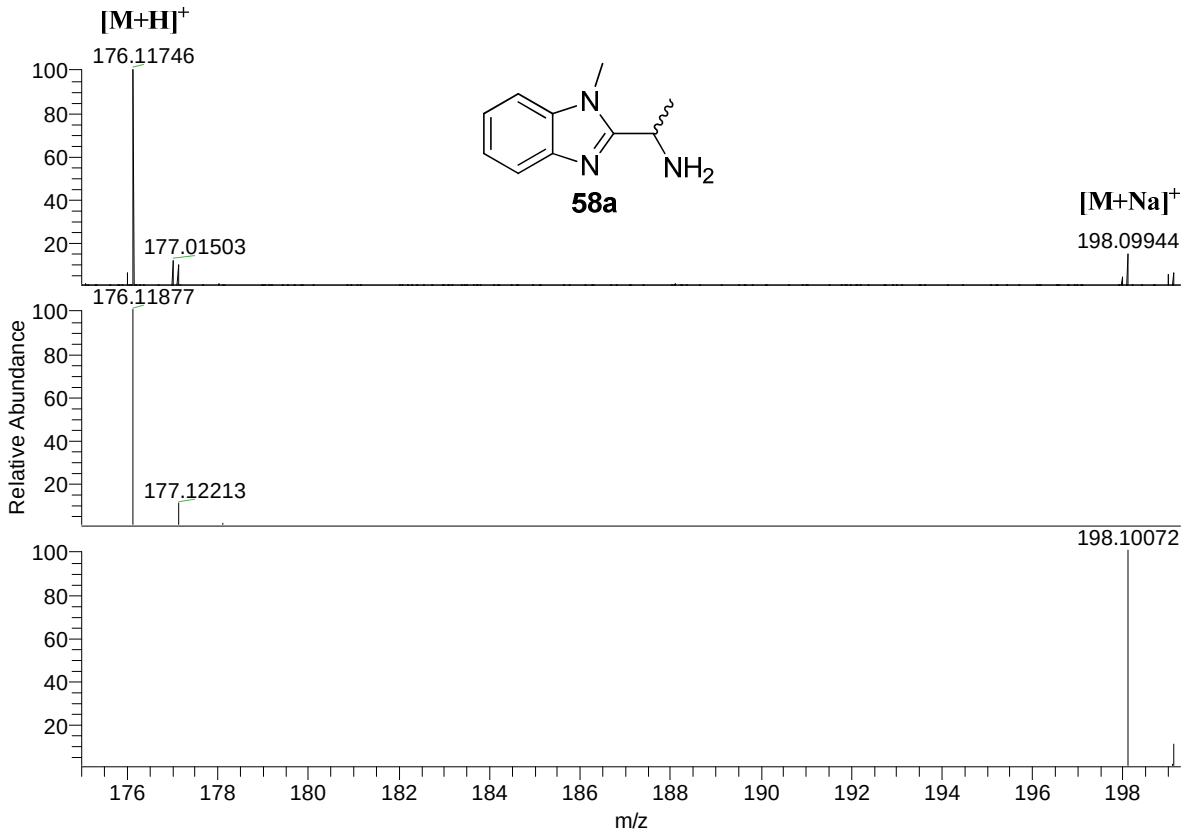
ATTACHMENTS



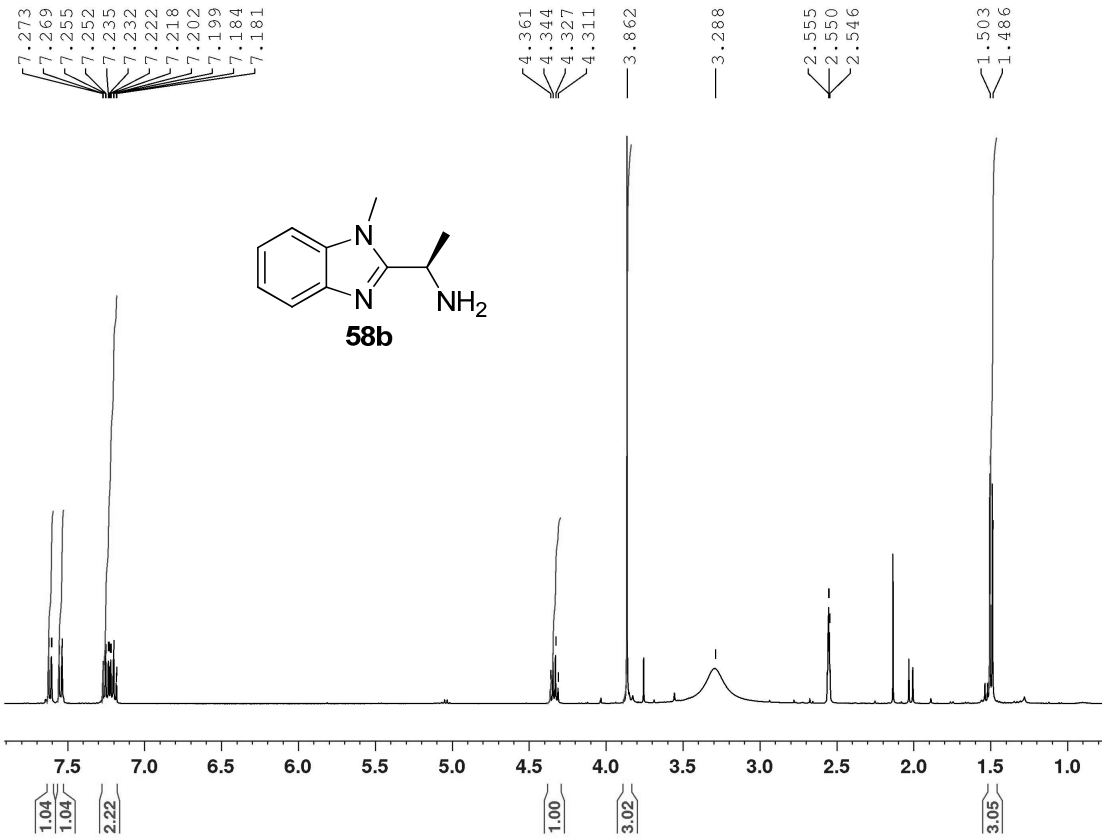
Attachment 1. *^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of catalyst* ***58a****.*



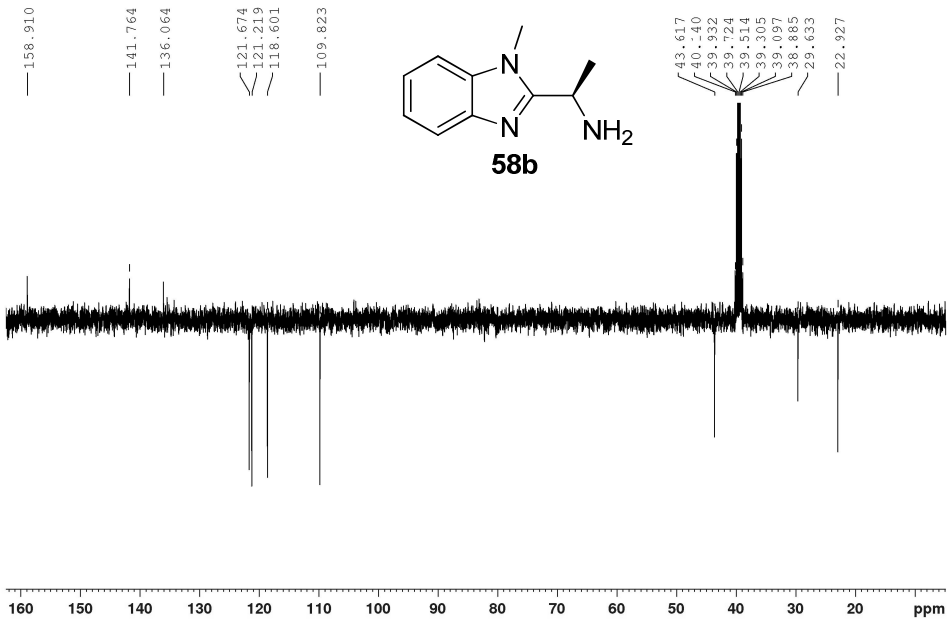
Attachment 2. *^{13}C-APT NMR (DMSO-d_6, 100MHz) spectrum of catalyst* ***58a****.*



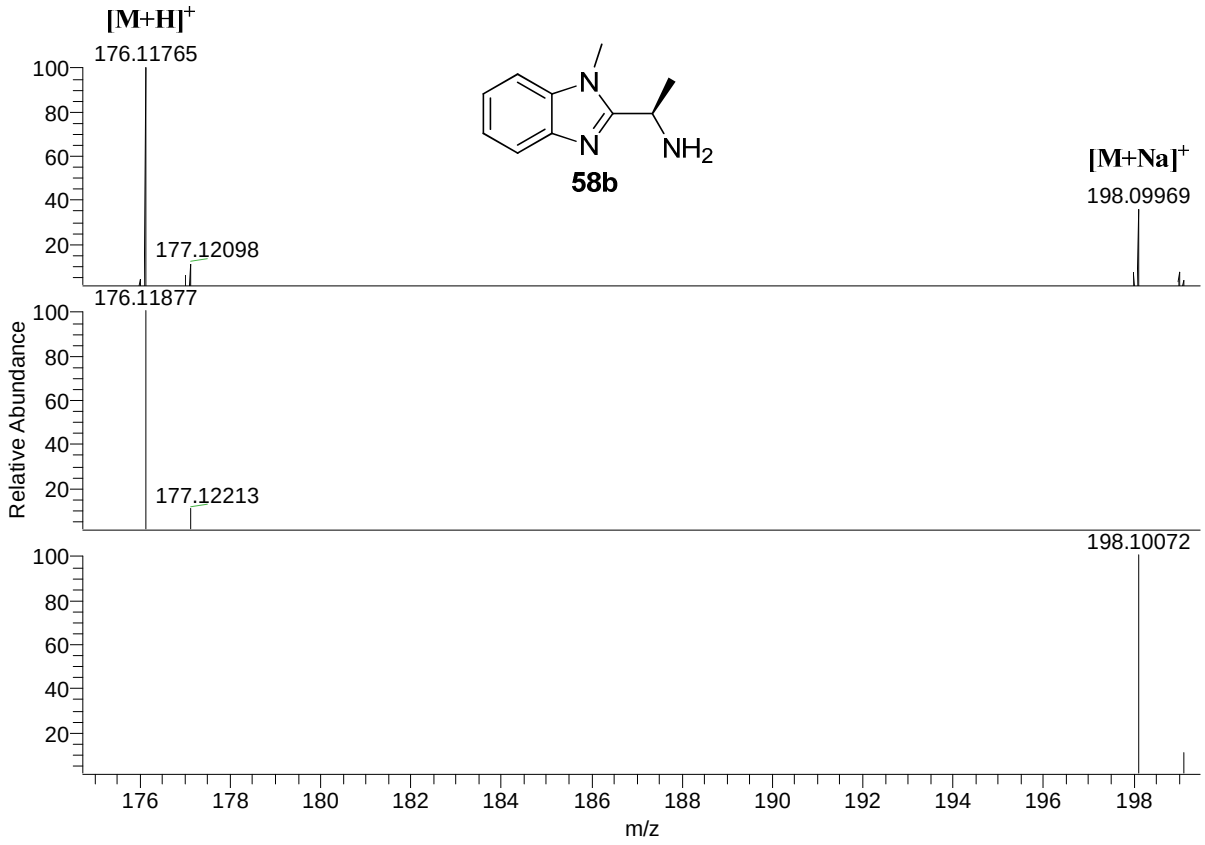
Attachment 3. *Experimental (up) calculated (down) MALDI spectrum of catalyst* ***58a****.*



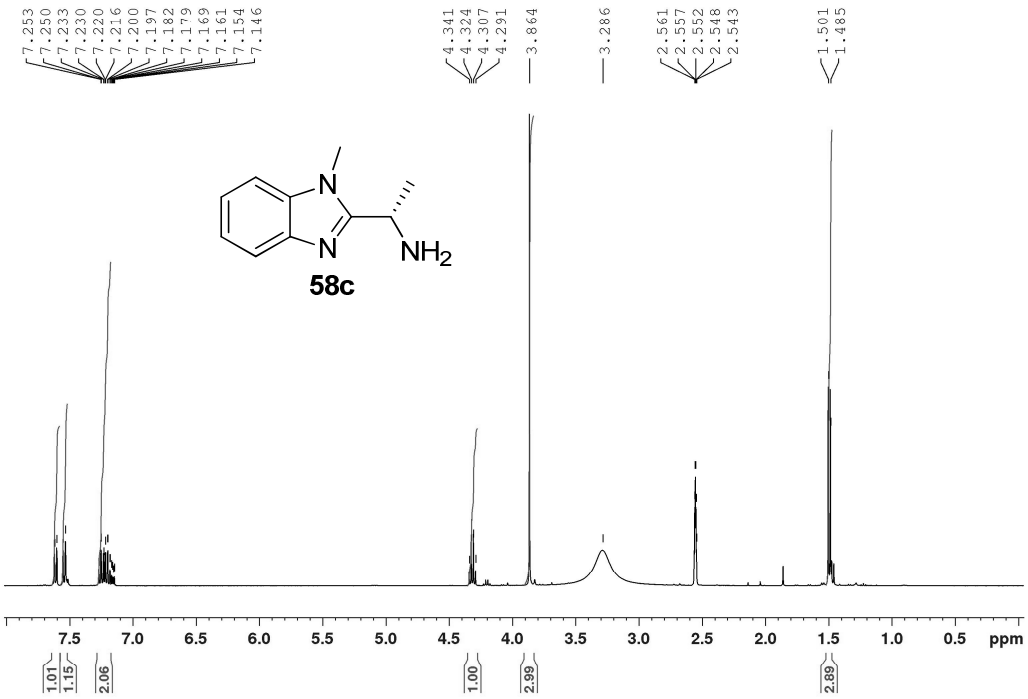
Attachment 4. *^{1}H NMR (DMSO-d_6, 400MHz) spectrum of catalyst **58b**.*



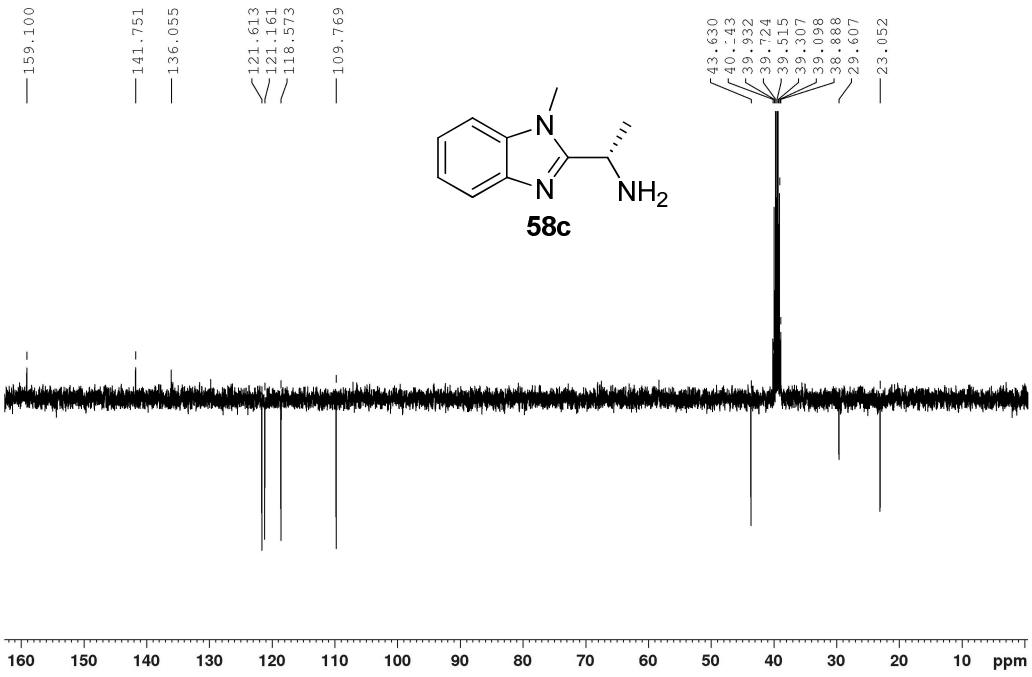
Attachment 5. *^{13}C-APT NMR (DMSO-d_6, 100MHz) spectrum of catalyst **58b**.*



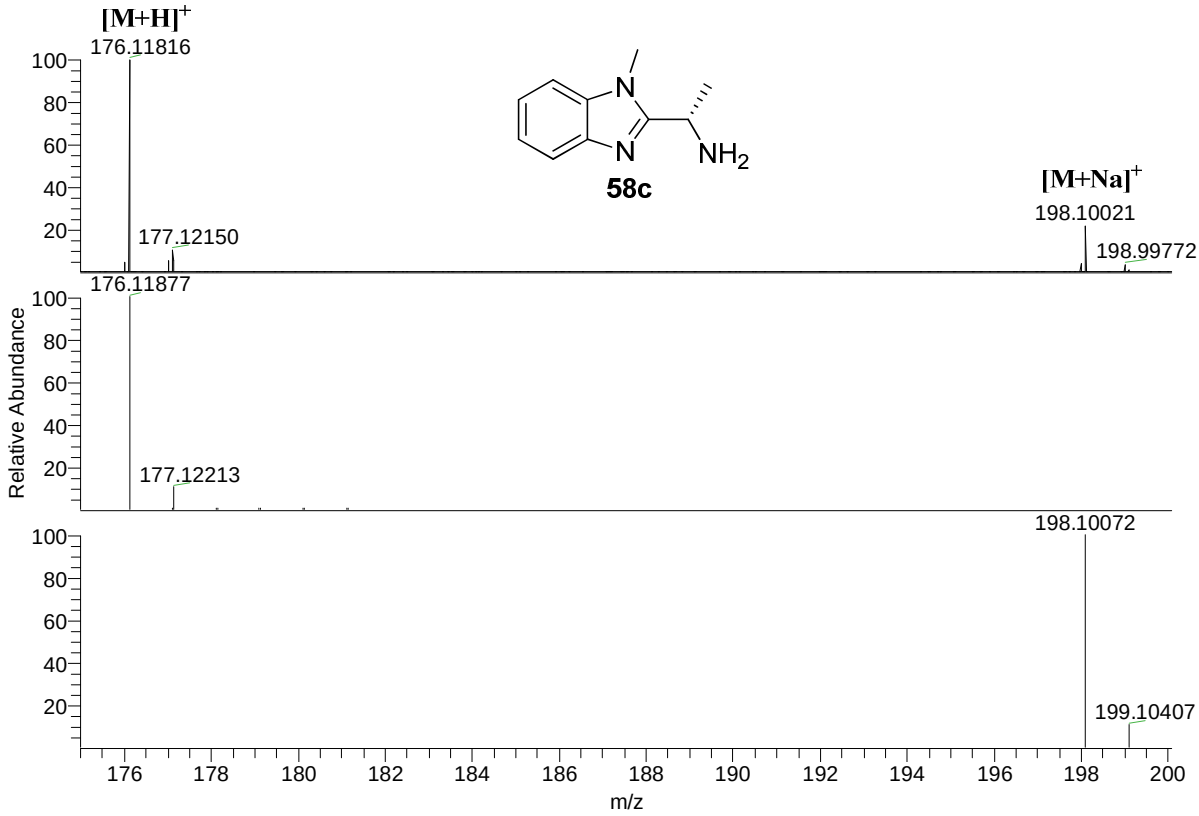
***Attachment 6**. Experimental (up) calculated (down) MALDI spectrum of catalyst **58b**.*



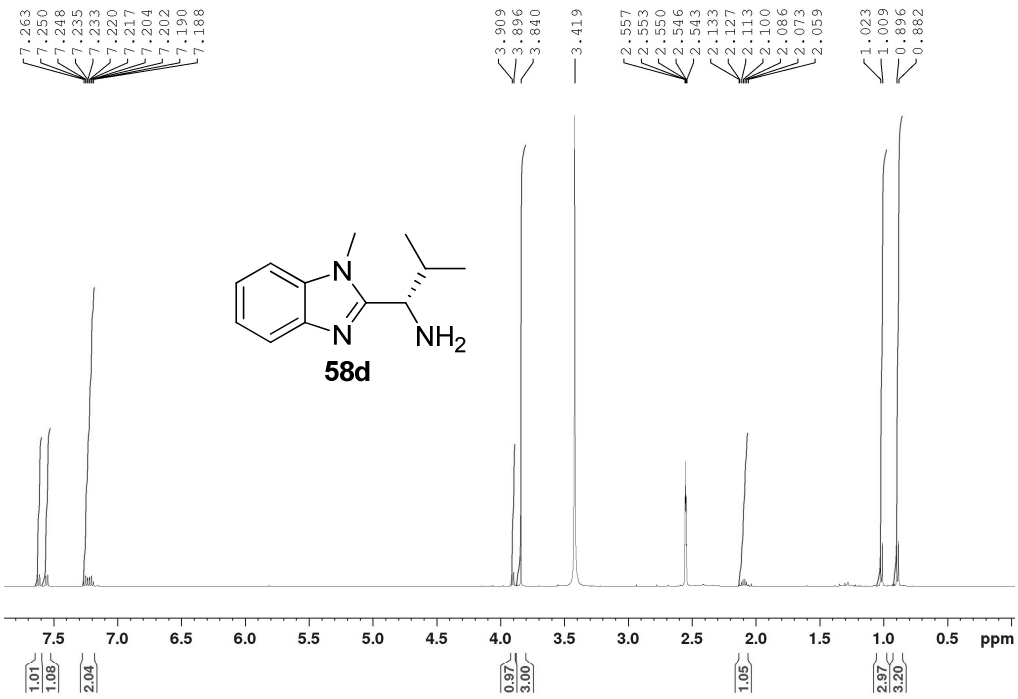
Attachment 7. *^{1}H NMR (DMSO-d_6, 400MHz) spectrum of catalyst* ***58c****.*



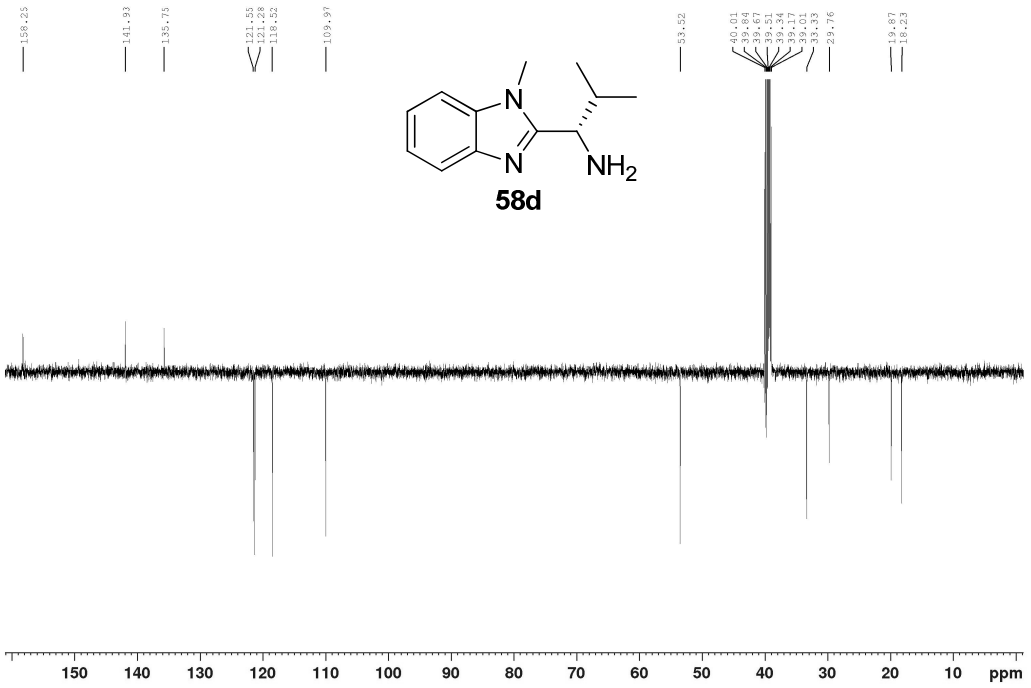
Attachment 8. *^{13}C-APT NMR (DMSO-d_6, 100MHz) spectrum of catalyst* ***58c****.*



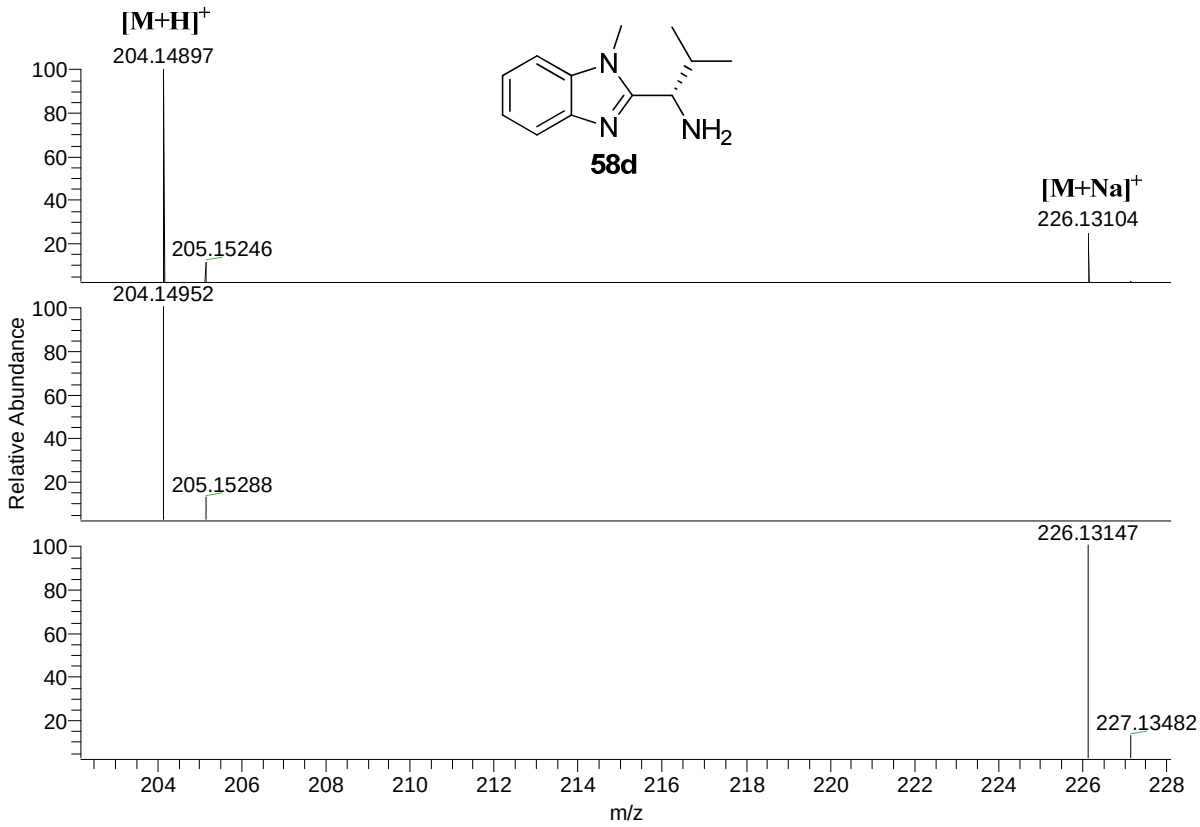
Attachment 9. *Experimental (up) calculated (down) MALDI spectrum of catalyst* ***58c****.*



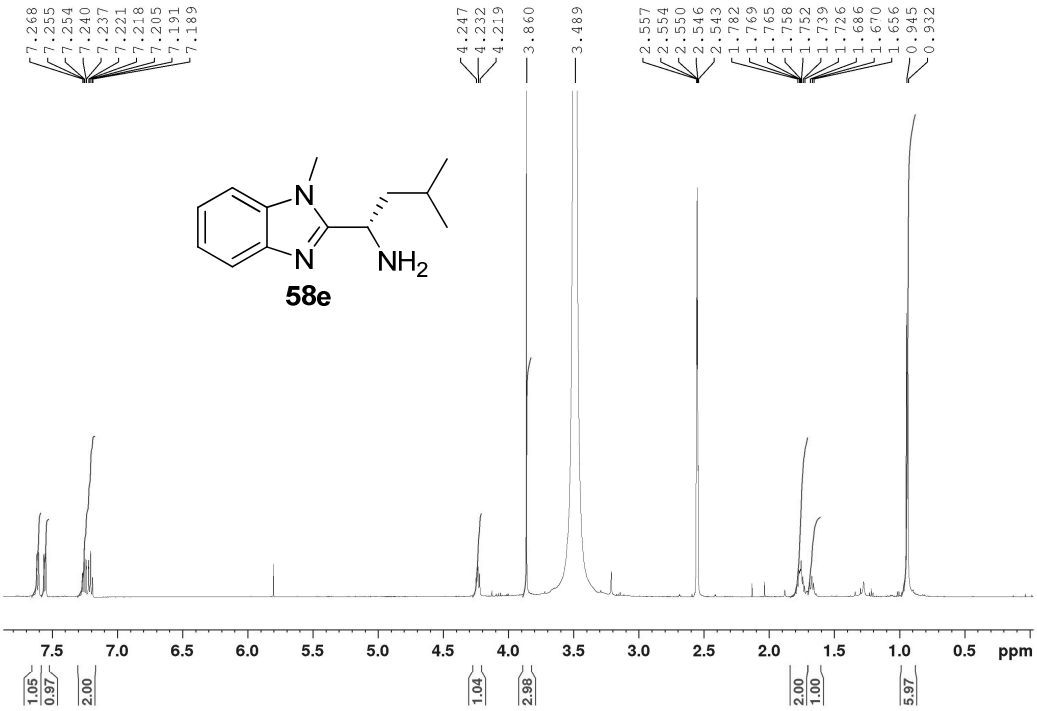
Attachment 10. *^{1}H NMR (DMSO-d_6, 500MHz) spectrum of catalyst* ***58d****.*



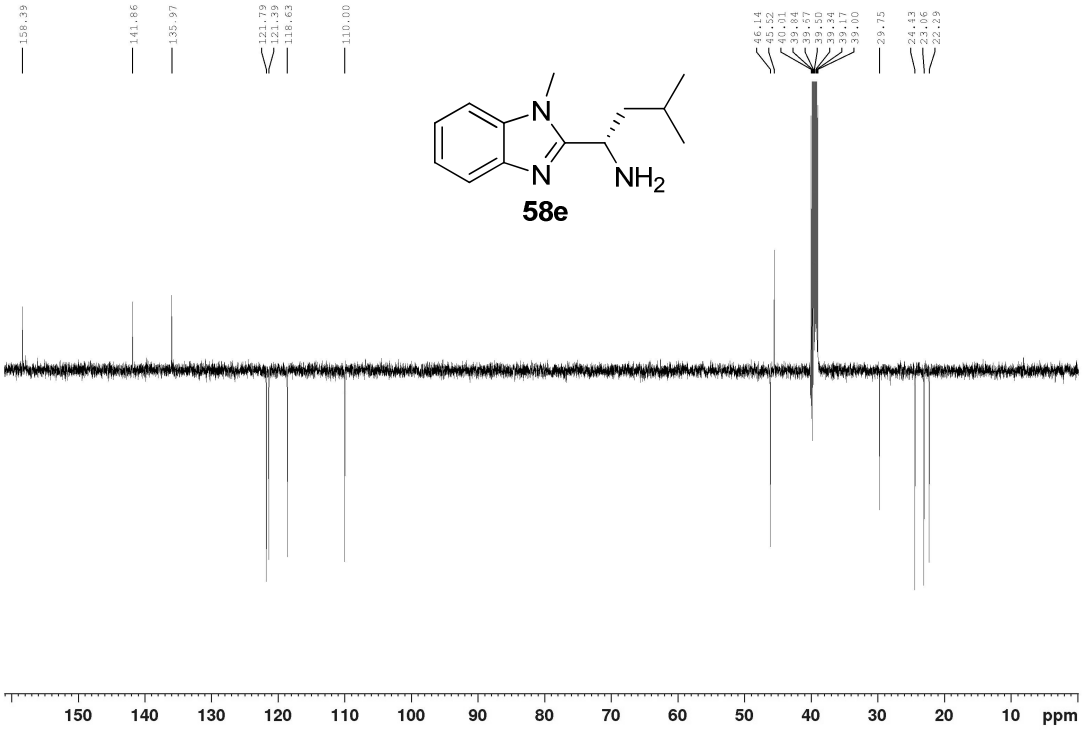
Attachment 11. *^{13}C-APT NMR (DMSO-d_6, 125MHz) spectrum of catalyst* ***58d****.*



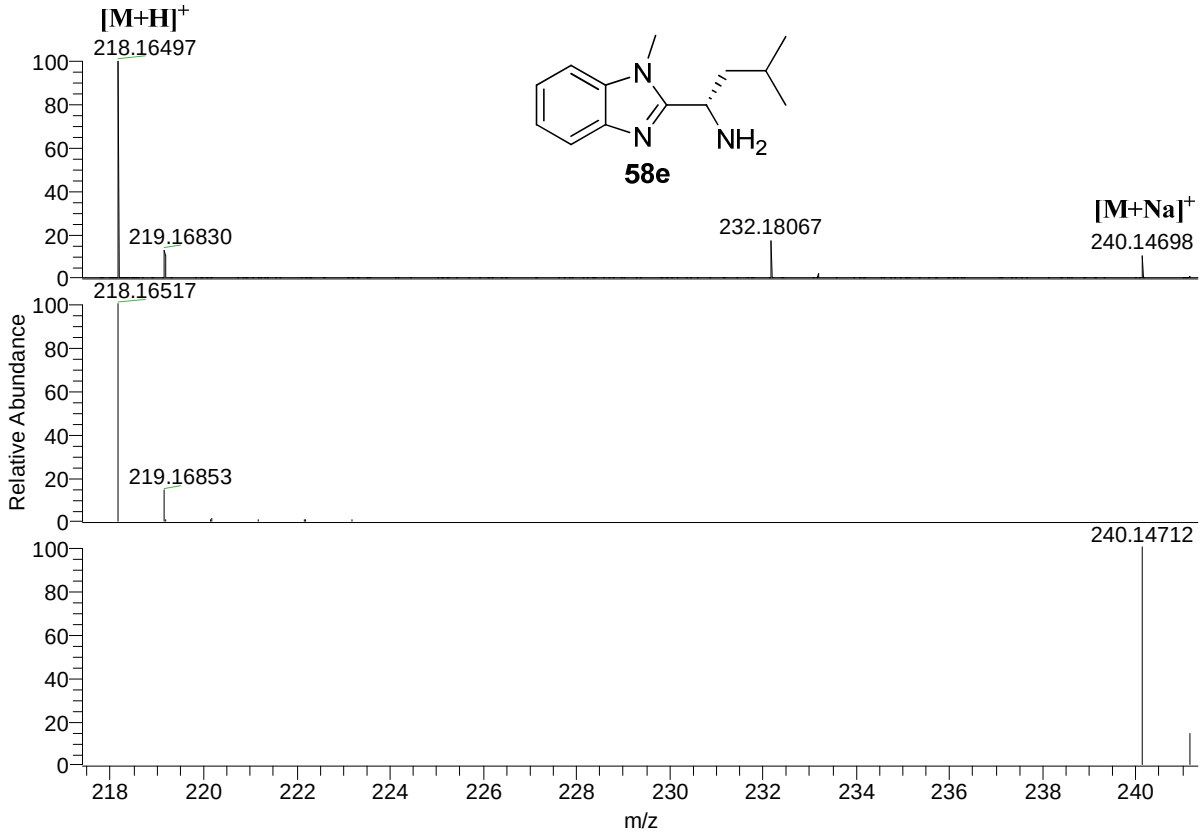
Attachment 12. *Experimental (up) calculated (down) MALDI spectrum of catalyst* ***58d****.*



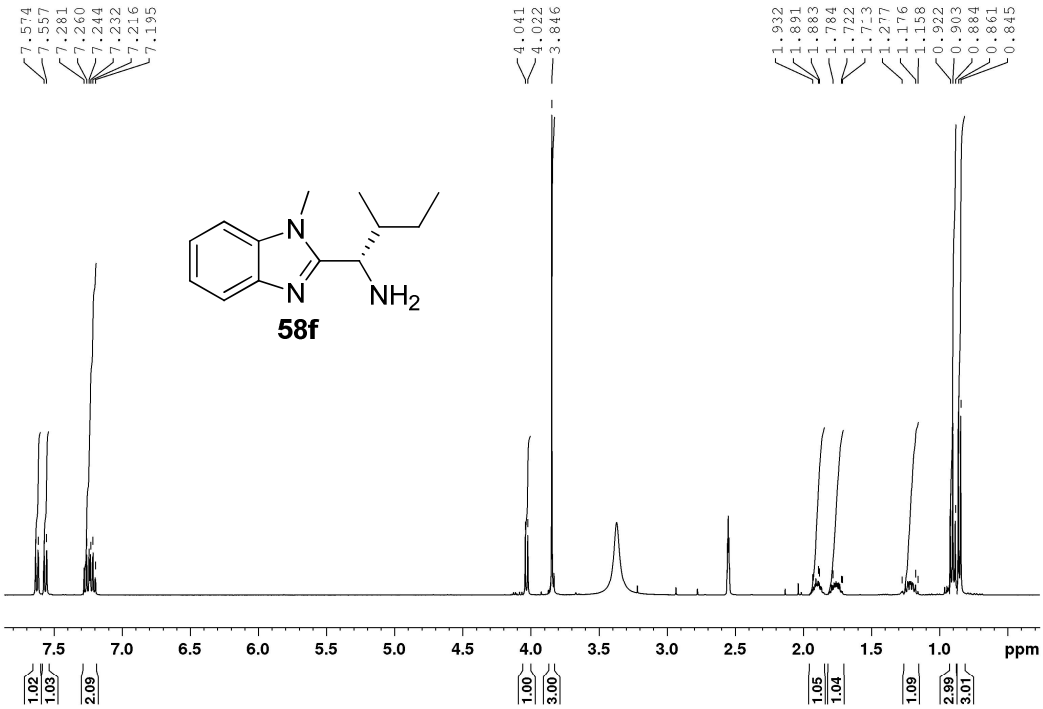
Attachment 13. *^{1}H NMR (DMSO-d_6, 500MHz) spectrum of catalyst* ***58e****.*



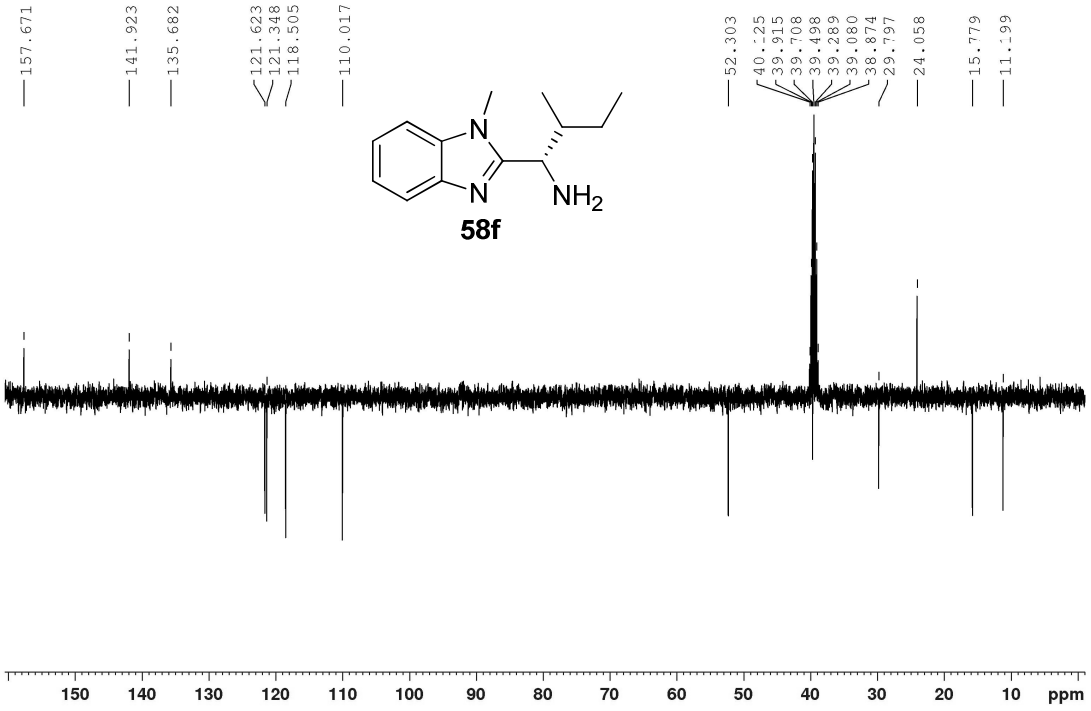
Attachment 14. *^{13}C-APT NMR (DMSO-d_6, 125MHz) spectrum of catalyst* ***58e****.*



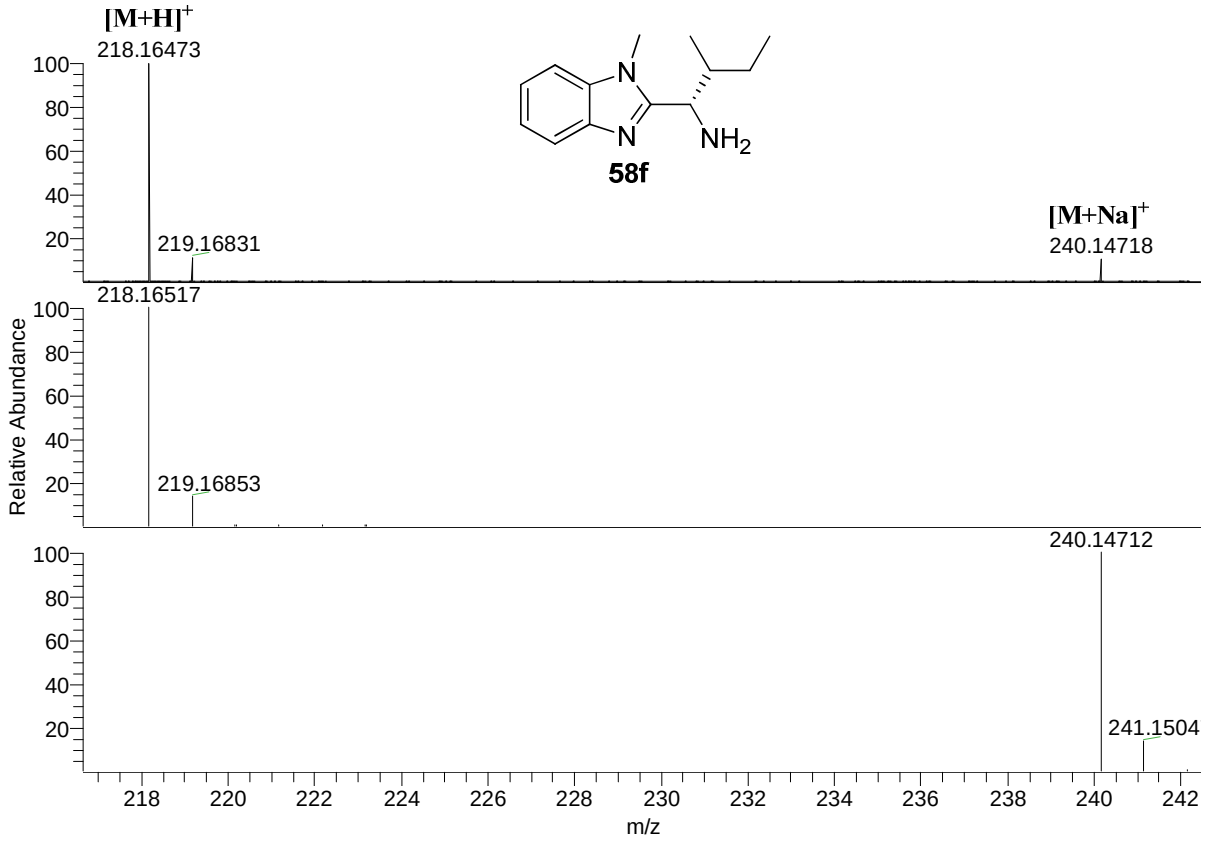
***Attachment 15**. Experimental (up) calculated (down) MALDI spectrum of catalyst **58e**.*



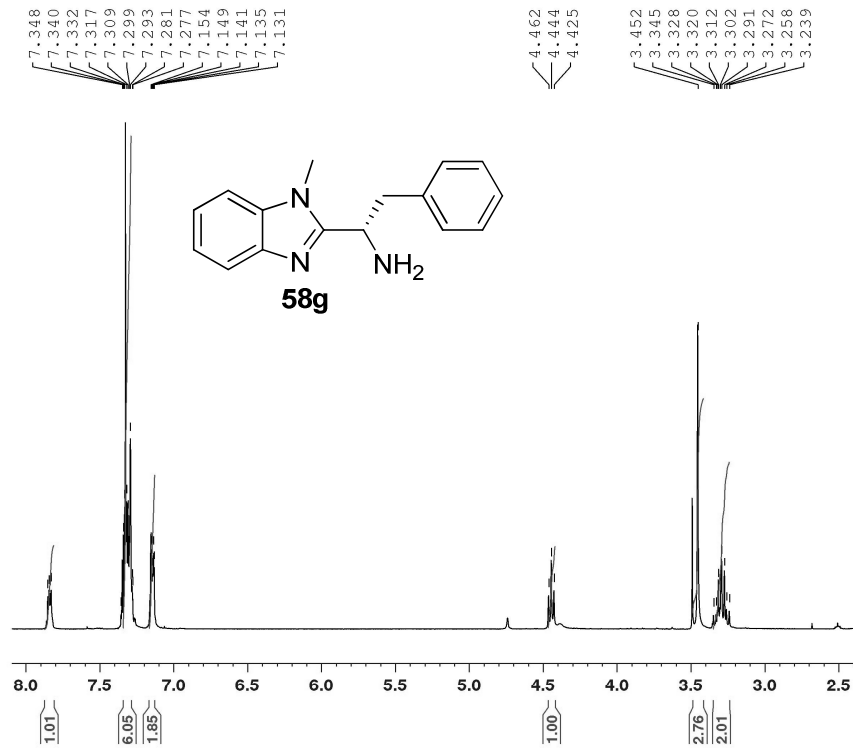
Attachment 16. *^{1}H NMR (DMSO-d_6, 400MHz) spectrum of catalyst* ***58f****.*



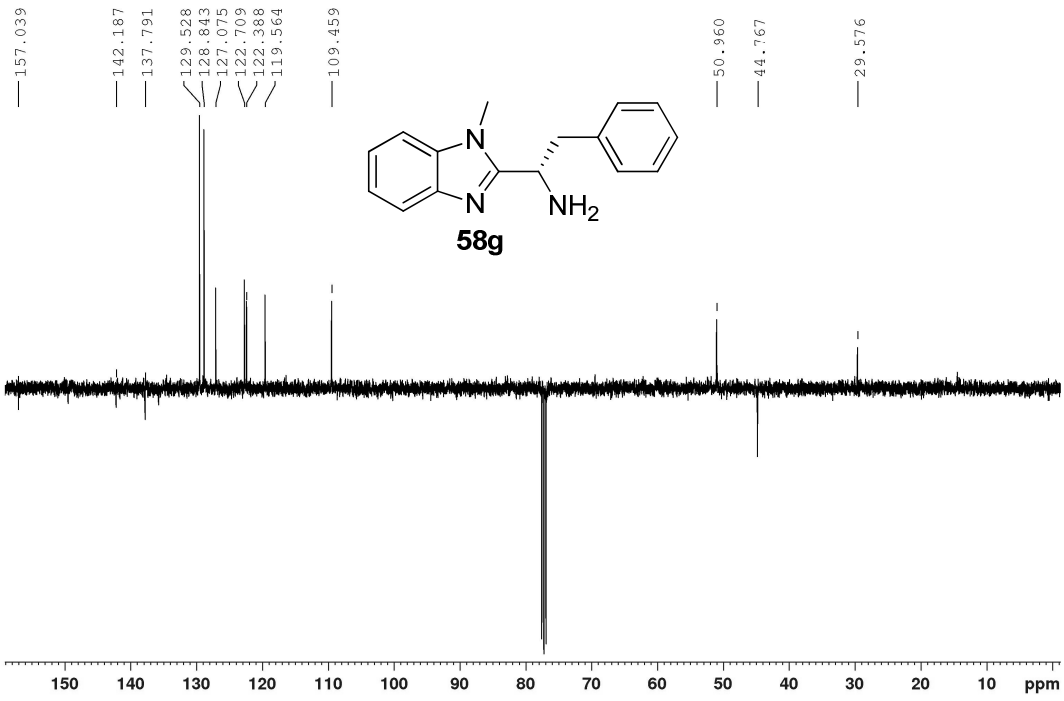
Attachment 17. *^{13}C NMR (DMSO-d_6, 100MHz) spectrum of catalyst* ***58f****.*



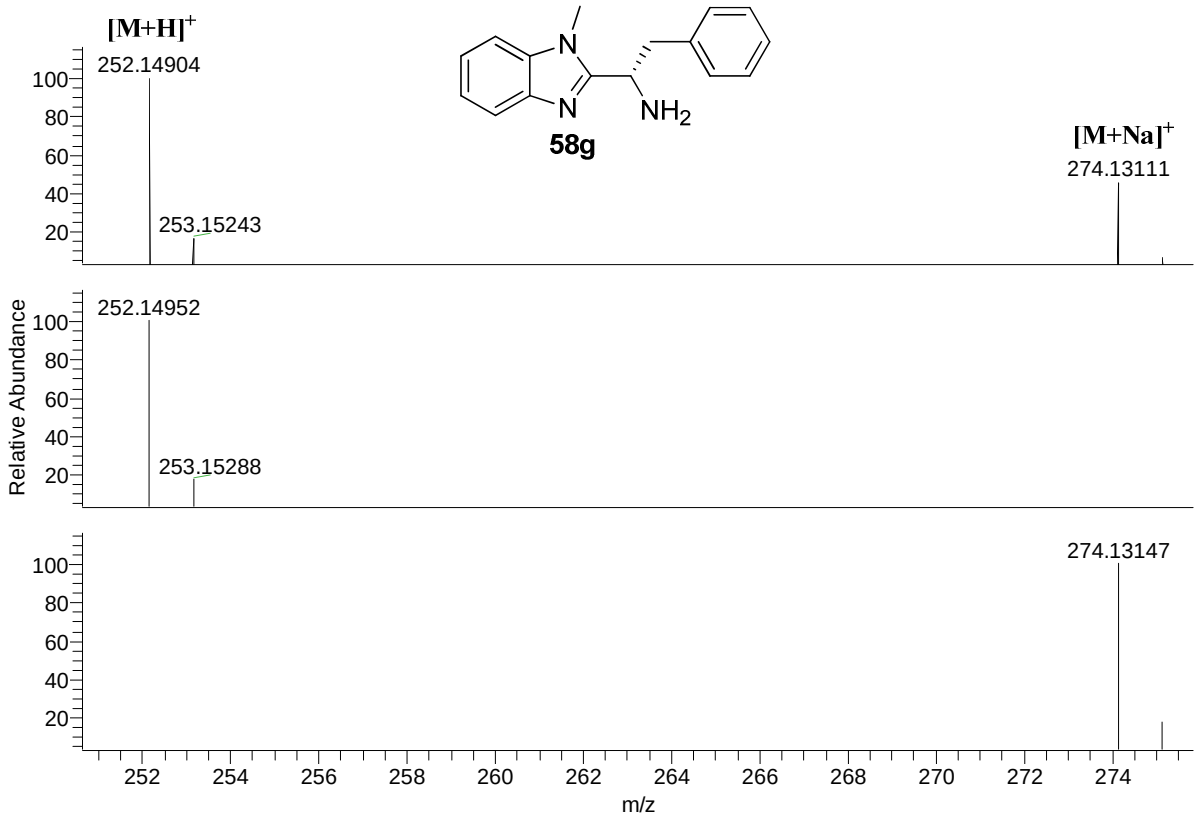
Attachment 18. *Experimental (up) calculated (down) MALDI spectrum of catalyst* ***58f****.*



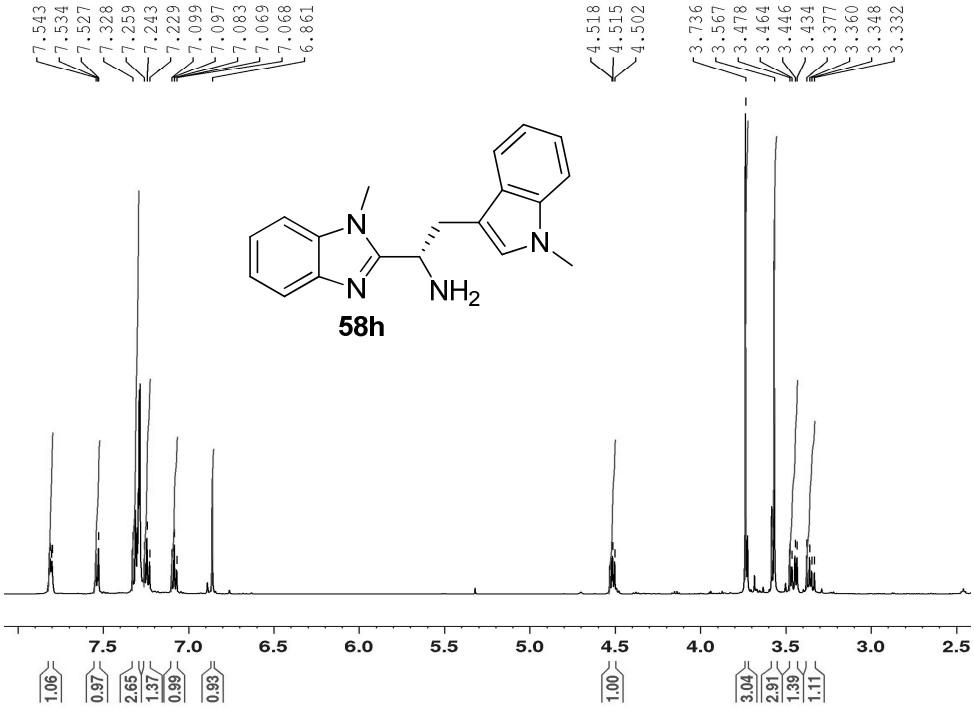
Attachment 19. *^{1}H NMR ($CDCl_3$, 400MHz) spectrum of catalyst* ***58g****.*



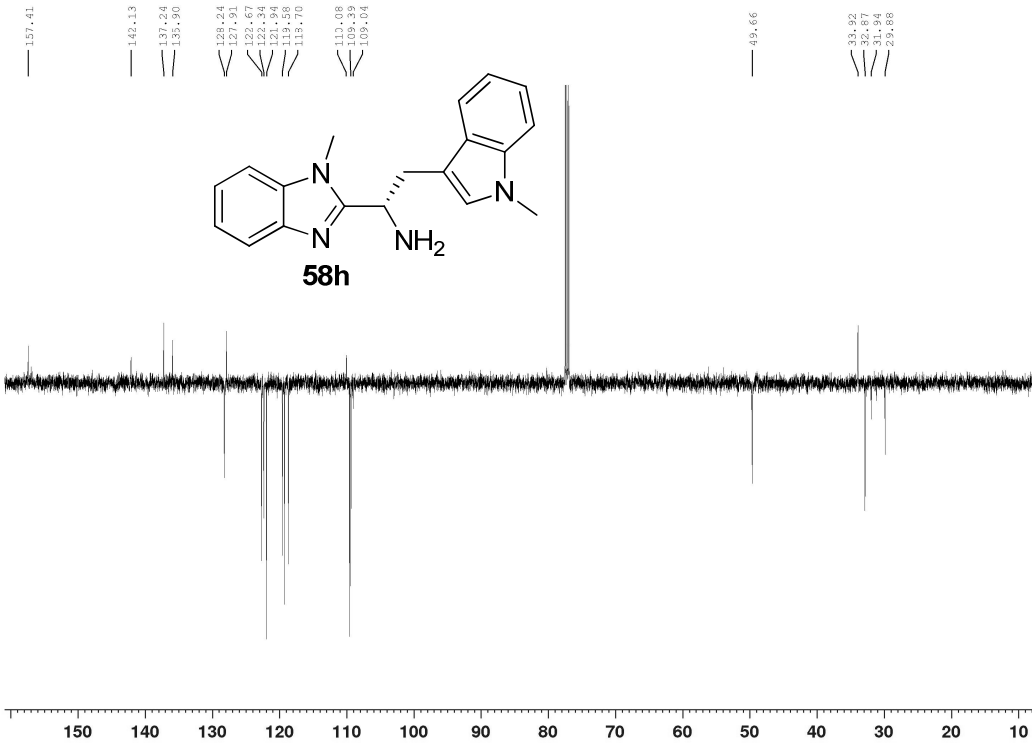
Attachment 20. *^{13}C-APT NMR ($CDCl_3$, 100MHz) spectrum of catalyst* ***58g****.*



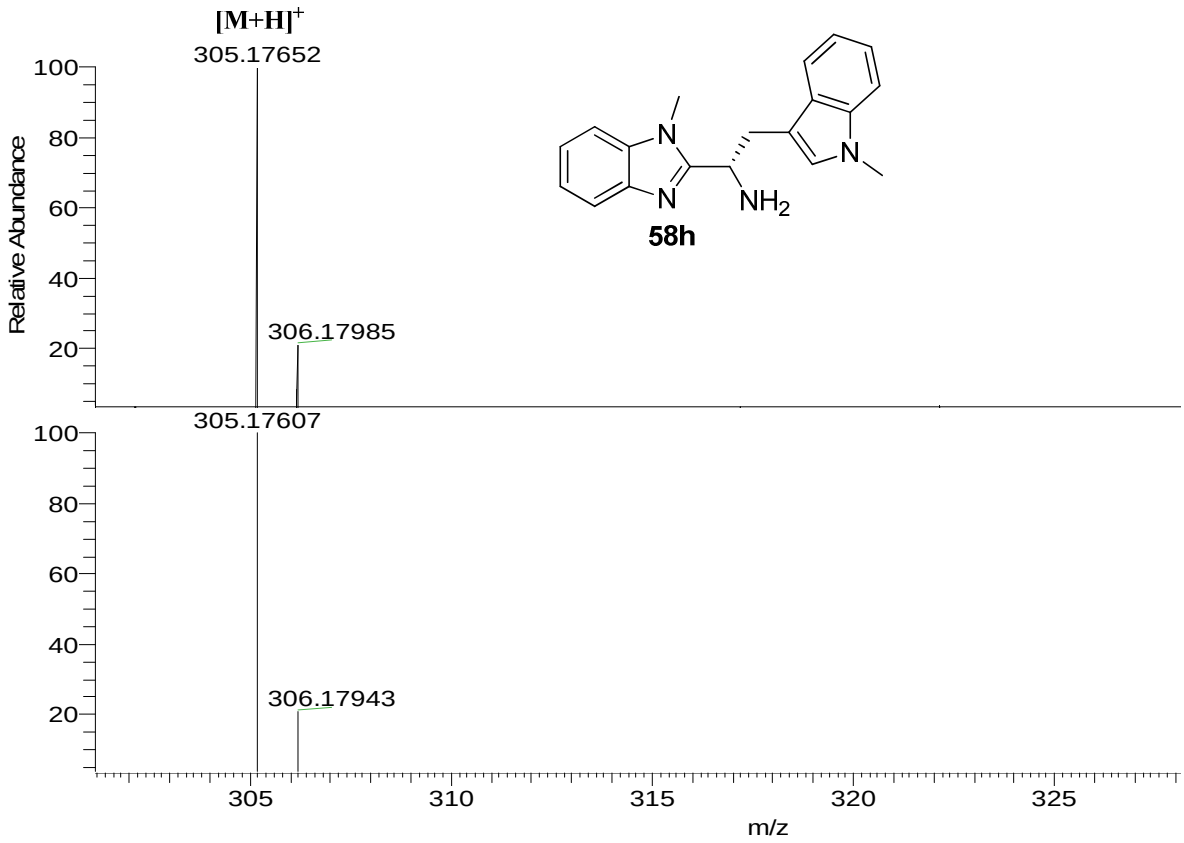
Attachment 21. *Experimental (up) calculated (down) MALDI spectrum of catalyst* ***58g****.*



Attachment 22. *^{1}H NMR ($CDCl_3$, 500MHz) spectrum of catalyst* ***58h*****.**

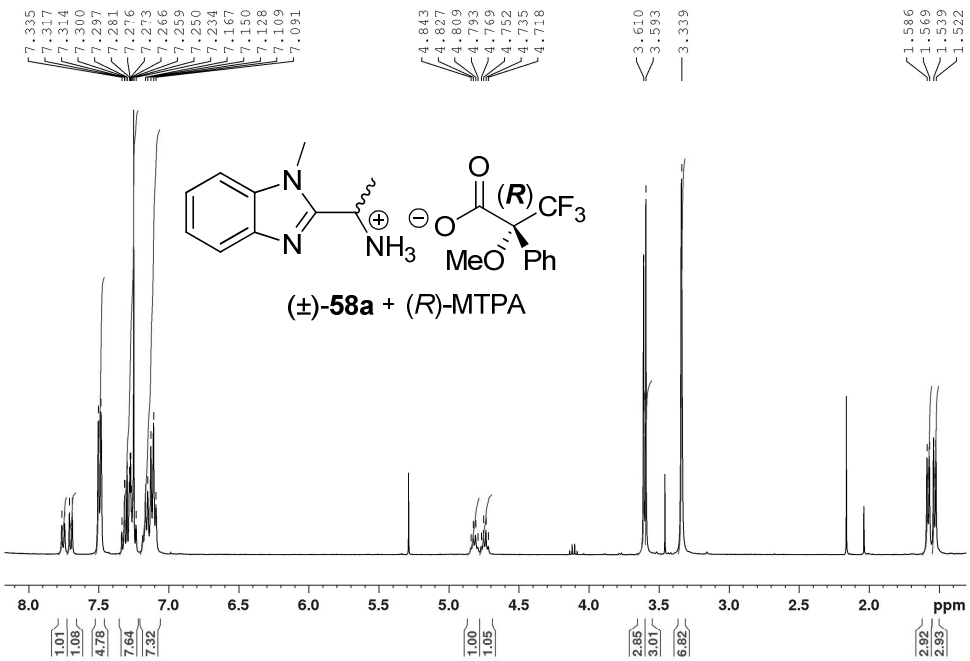


Attachment 23. *^{13}C-APT NMR ($CDCl_3$, 125MHz) spectrum of catalyst* ***58h*****.**

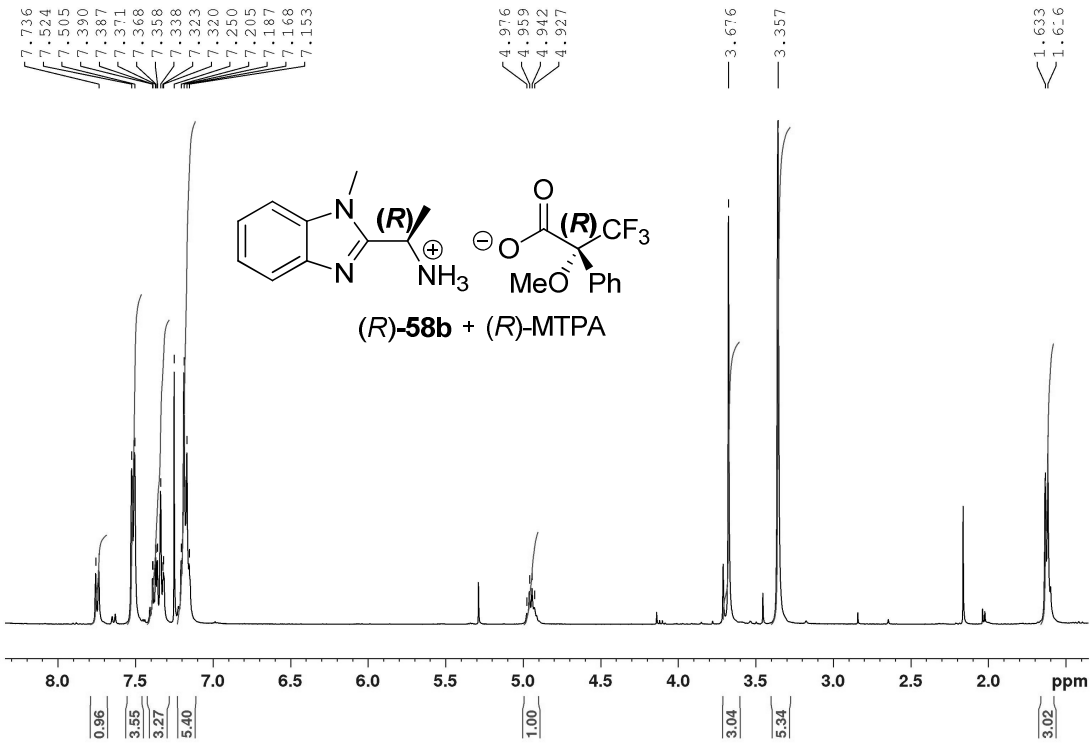


Attachment 24. *Experimental (up) calculated (down) MALDI spectrum of catalyst* ***58h*****.**

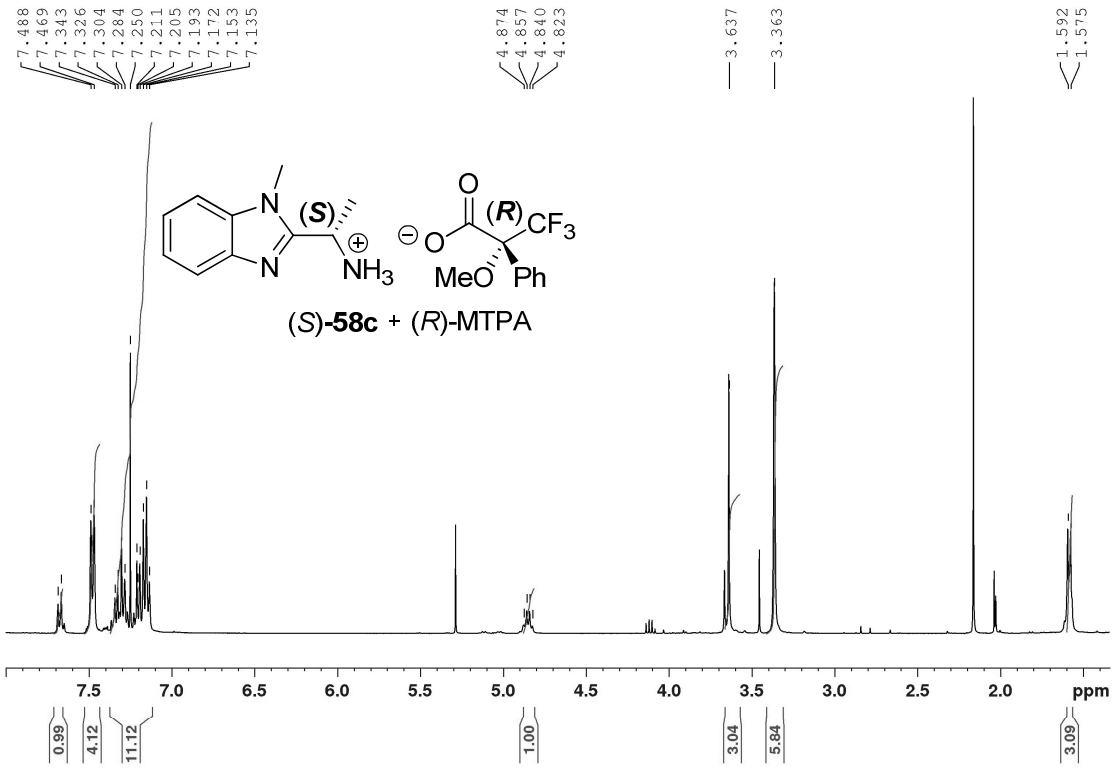
^{1}H NMR spectra of catalysts 58a-h measured with Mosher's acid.



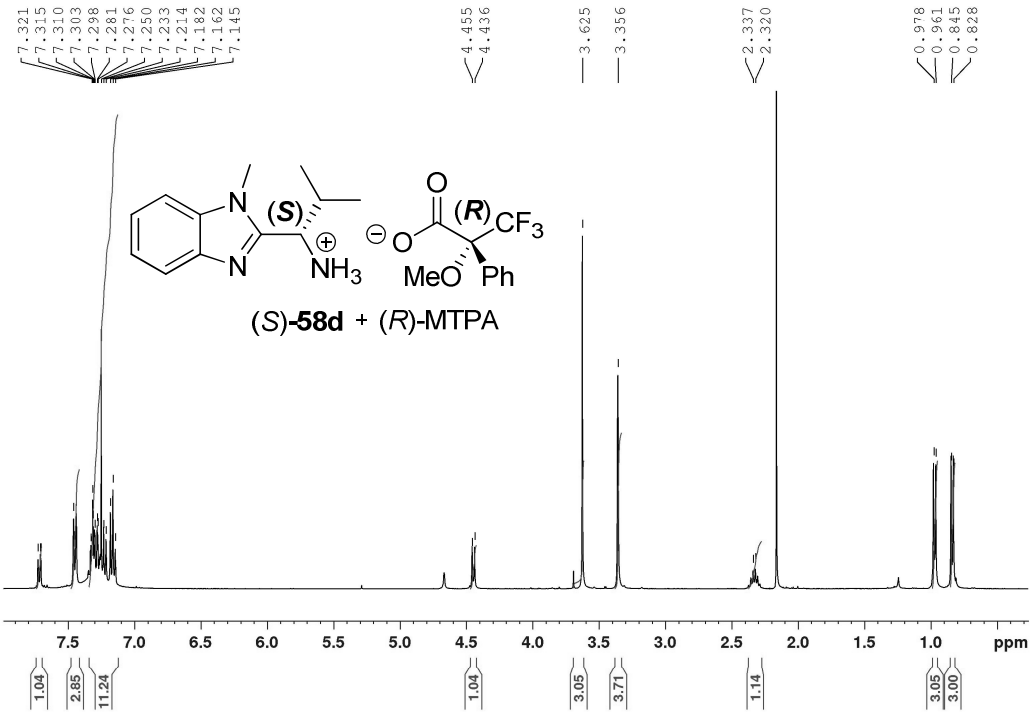
Attachment 25. *^{1}H NMR ($CDCl_3$, 400MHz) spectrum of catalyst (±)-**58a** measured with Mosher's acid.*



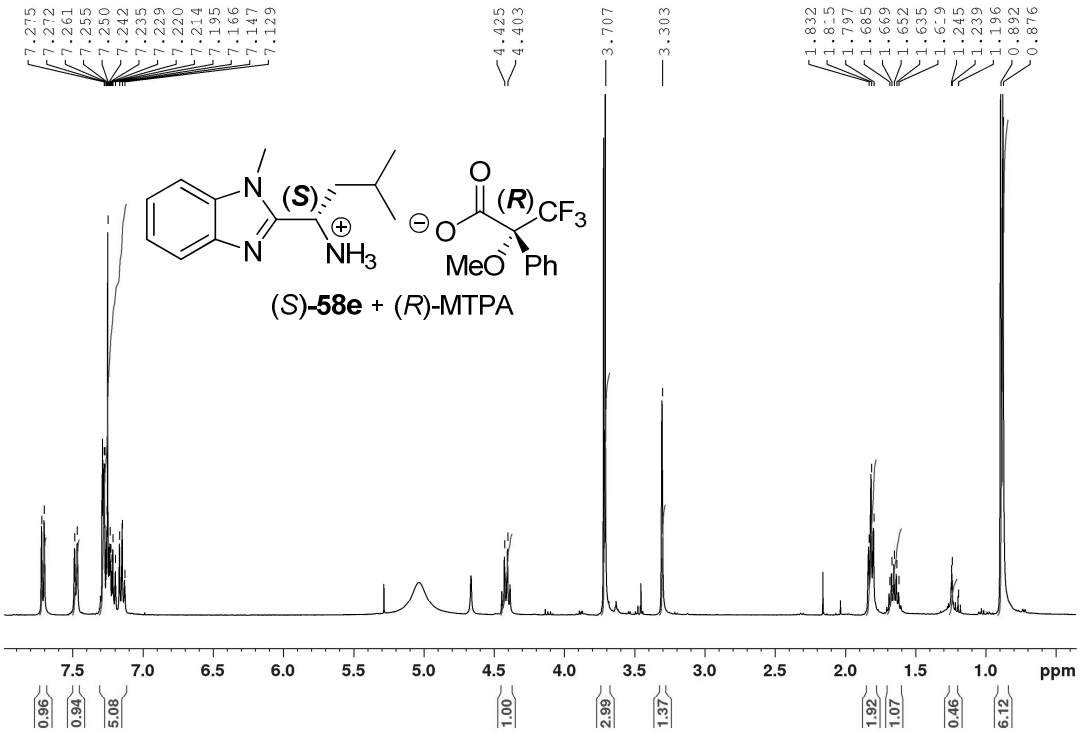
Attachment 26. *^{1}H NMR ($CDCl_3$, 400MHz) spectrum of catalyst (R)-**58b** measured with Mosher's acid.*



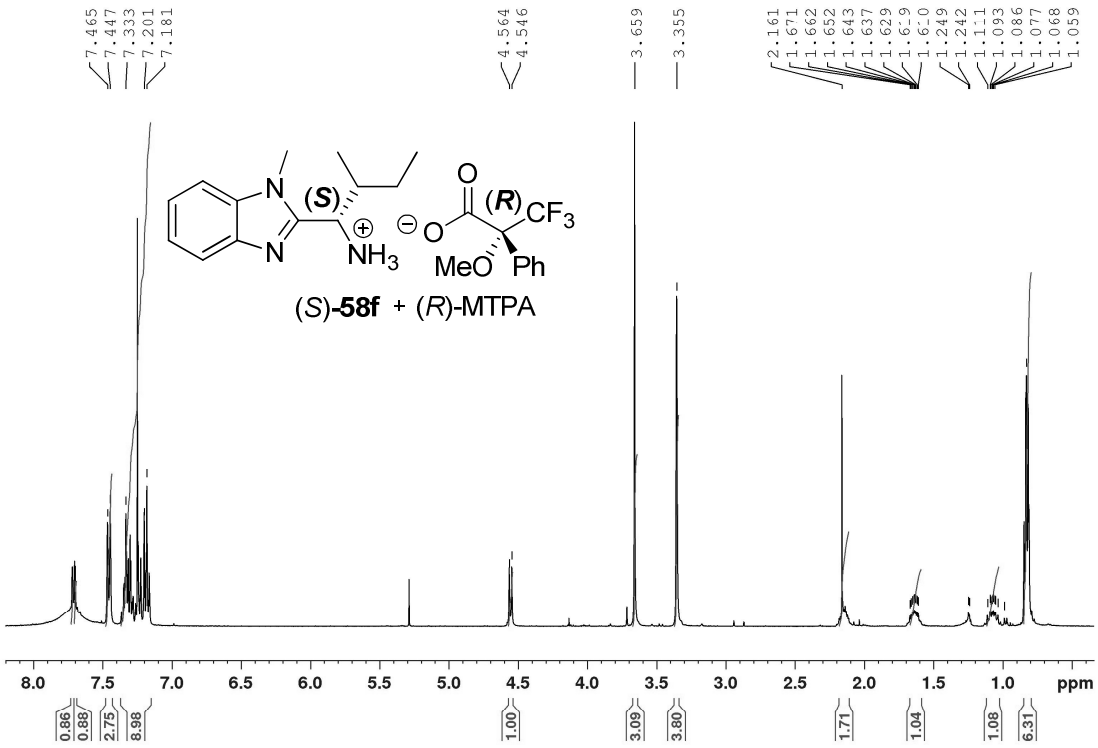
Attachment 27. *^{1}H NMR ($CDCl_3$, 400MHz) spectrum of catalyst (S)-**58c** measured with Mosher's acid.*



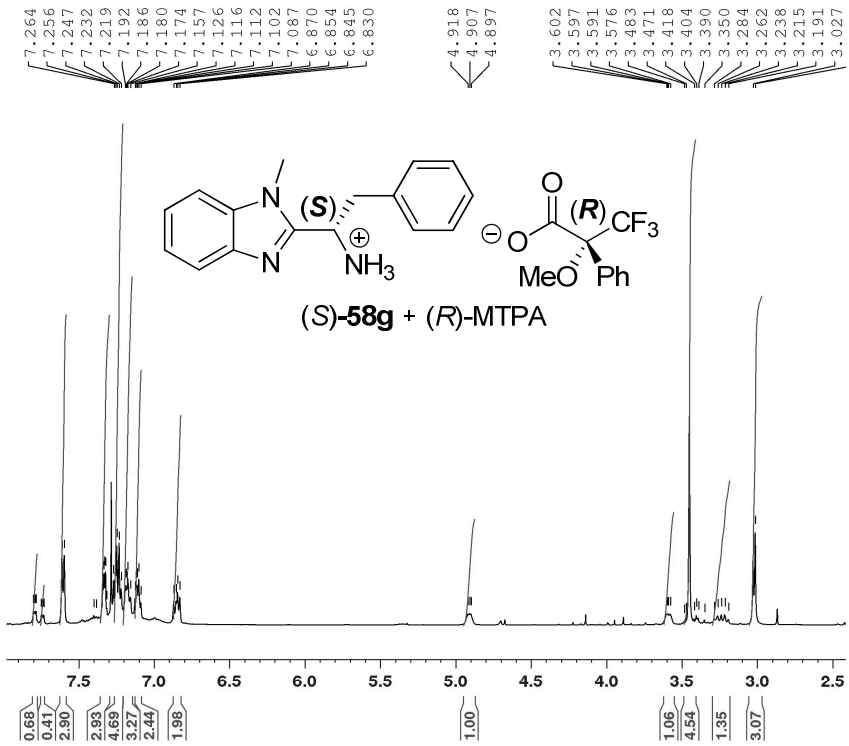
Attachment 28. *^{1}H NMR ($CDCl_3$, 400MHz) spectrum of catalyst (S)-**58d** measured with Mosher's acid.*



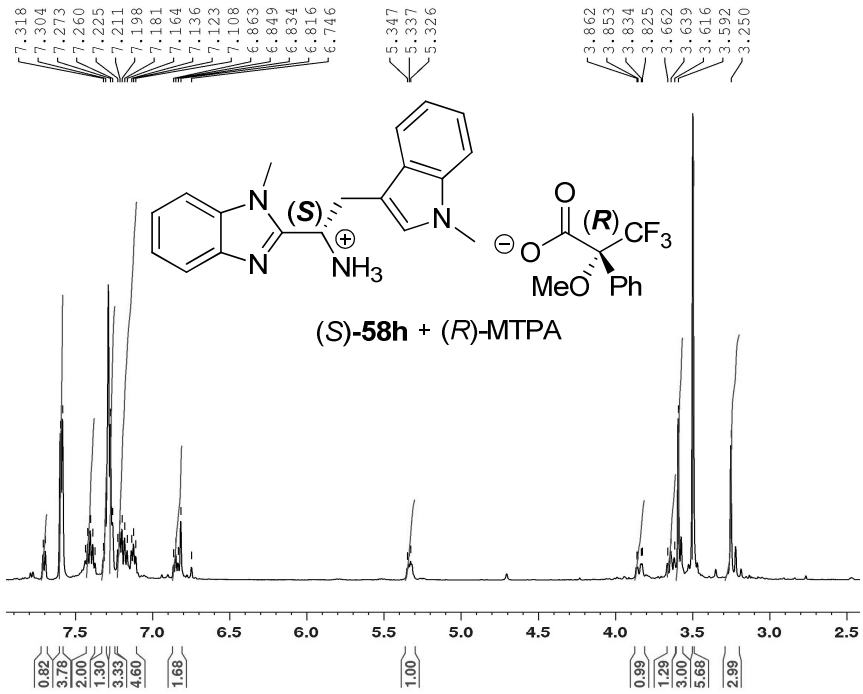
Attachment 29. *^{1}H NMR ($CDCl_3$, 400MHz) spectrum of catalyst (S)-**58e** measured with Mosher's acid.*



Attachment 30. *^{1}H NMR ($CDCl_3$, 400MHz) spectrum of catalyst (S)-**58f** measured with Mosher's acid.*



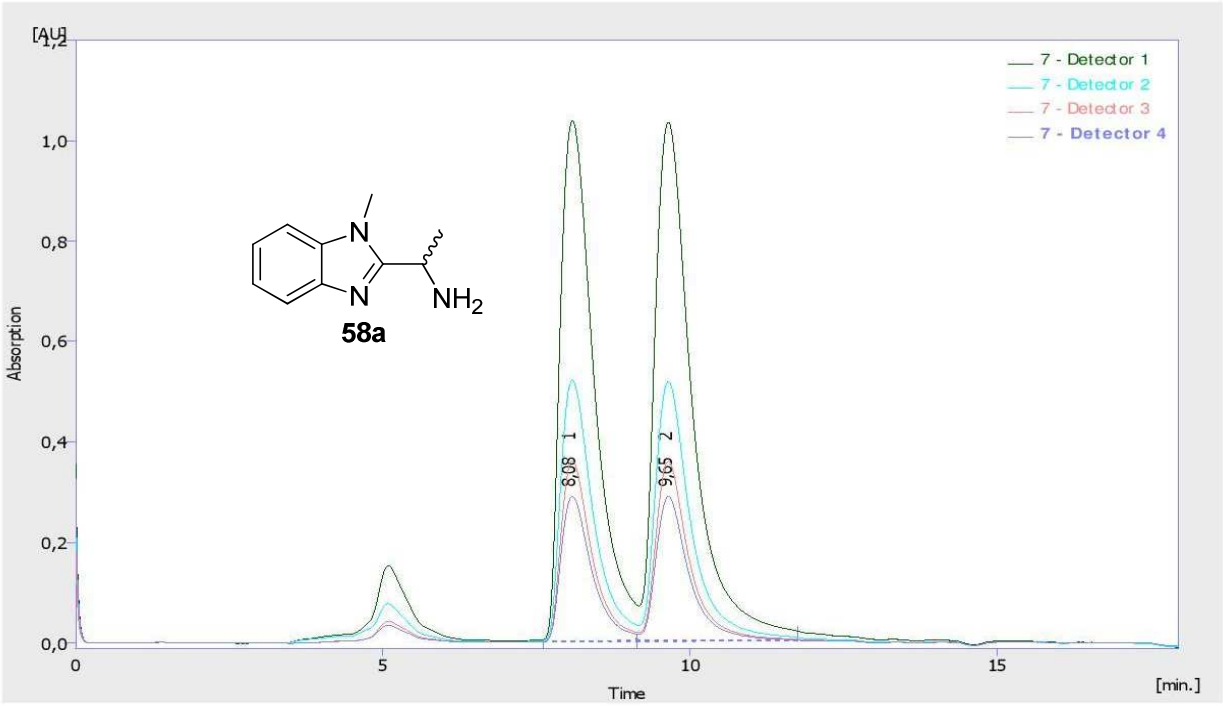
Attachment 31. *^{1}H NMR ($CDCl_3$, 400MHz) spectrum of catalyst (S)-**58g** measured with Mosher's acid.*



Attachment 32. *^{1}H NMR ($CDCl_3$, 400MHz) spectrum of catalyst (S)-**58h** measured with Mosher's acid.*

Clarity - Chromatography SW
DataApex
www.dataapex.com

Method	: benzimidazol	By	: Administrator
Description	:		
Created	: 3.12.2013 13:54	Modified	: 6.12.2013 11:00
Column	:	Detection	:
Mobile Phase	:	Temperature	:
Flow Rate	:	Pressure	:
Note	:		



Result Table (Uncal - 7 - Detector 4)

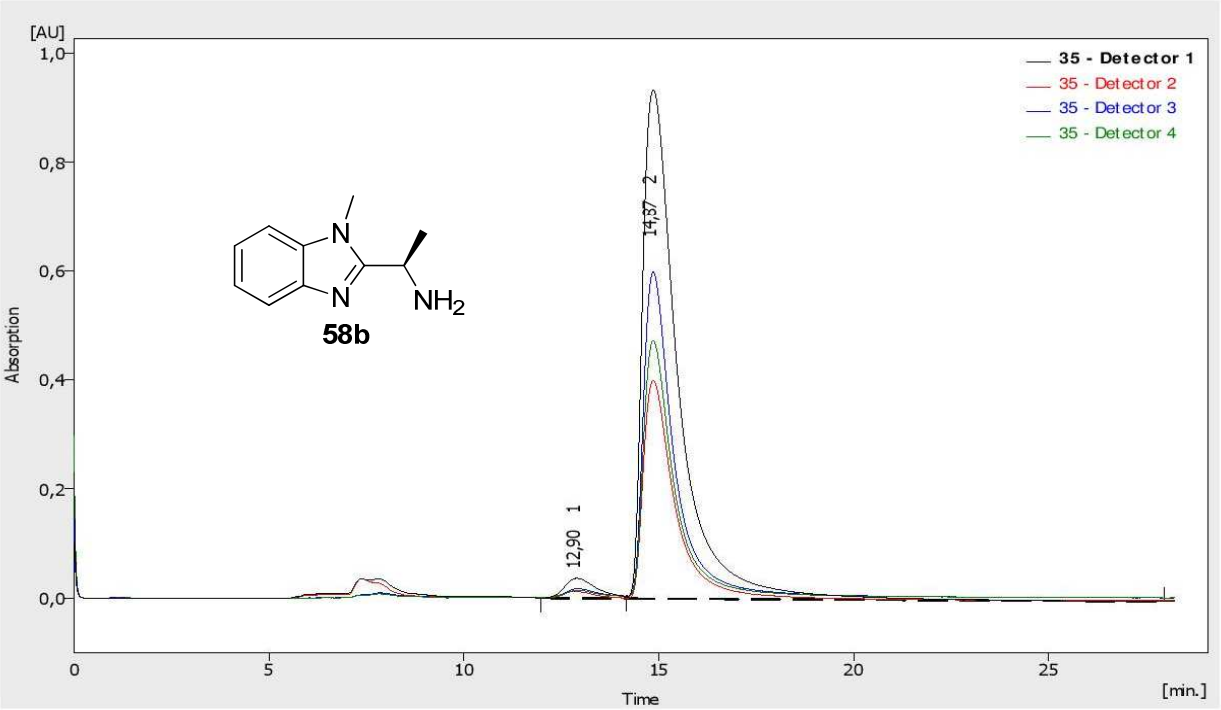
	Reten. Time [min]	Area [mAU.s]	Height [mAU]	Area [%]	Height [%]	W05 [min]	Peak Purity [-]
1	8,083	10059,246	287,616	48,1	50,1	0,53	970
2	9,650	10851,001	286,482	51,9	49,9	0,55	965
	Total	20910,247	574,098	100,0	100,0		

Attachment 33. *Chiral phase HPLC analysis of* ***58a*** *(Daicel Chiralcel OD-H, n-hexane/i-PrOH 70:30, flow rate 0.8 mL.min^{-1}, t_R = 8.08 min, t_R = 9.65 min). Estimated ee of 0%.*

Clarity - Chromatography SW
DataApex
www.dataapex.com

Sample Info:

Sample ID	: 1	Amount	: 0
Sample	: D-Ala benzimidazole	ISTD Amount	: 0
Inj. Volume [mL]	: 20	Dilution	: 1
Method	: benzimidazol	By	: Administrator
Description	: Methyl derivative		
Created	: 3.12.2013 13:54	Modified	: 12.2.2015 16:25
Column	: OD-H	Detection	:
Mobile Phase	: 30:70 iPrOH:hexane	Temperature	:
Flow Rate	:	Pressure	:
Note	:		



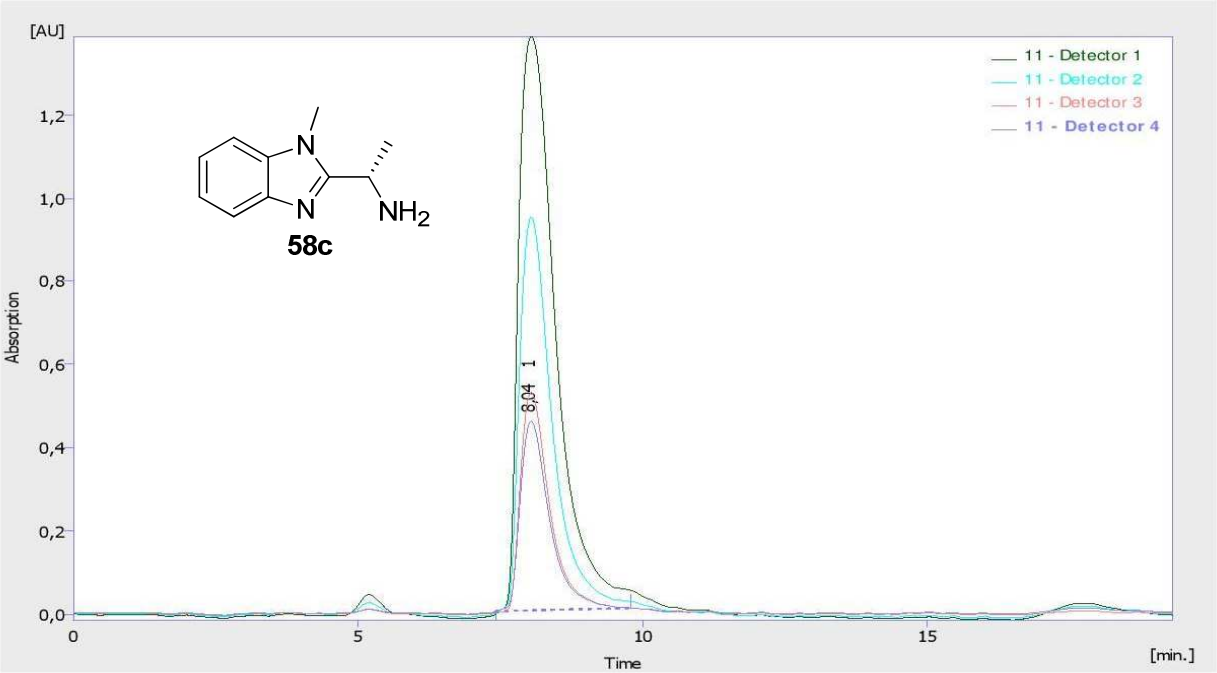
Result Table (Uncal - 35 - Detector 1)

	Reten. Time [min]	Area [mAU.s]	Height [mAU]	Area [%]	Height [%]	W05 [min]	Peak Purity [-]
1	12,900	2125,247	36,572	3,4	3,8	0,88	890
2	14,867	60208,569	934,679	96,6	96,2	0,88	605
	Total	62333,816	971,251	100,0	100,0		

Attachment 34. *Chiral phase HPLC analysis of* ***58b*** *(Daicel Chiralcel OD-H, n-hexane/i-PrOH 70:30, flow rate 0.8 mL.min^{-1}, t_R = 12.9 min, t_R = 14.8 min). Estimated ee of 95 %.*

Clarity - Chromatography SW
DataApex
www.dataapex.com

Method	: benzimidazol	By	: Administrator
Description	:		
Created	: 3.12.2013 13:54	Modified	: 6.12.2013 13:01
Column	:	Detection	:
Mobile Phase	:	Temperature	:
Flow Rate	:	Pressure	:
Note	:		



Result Table (Uncal - 11 - Detector 4)

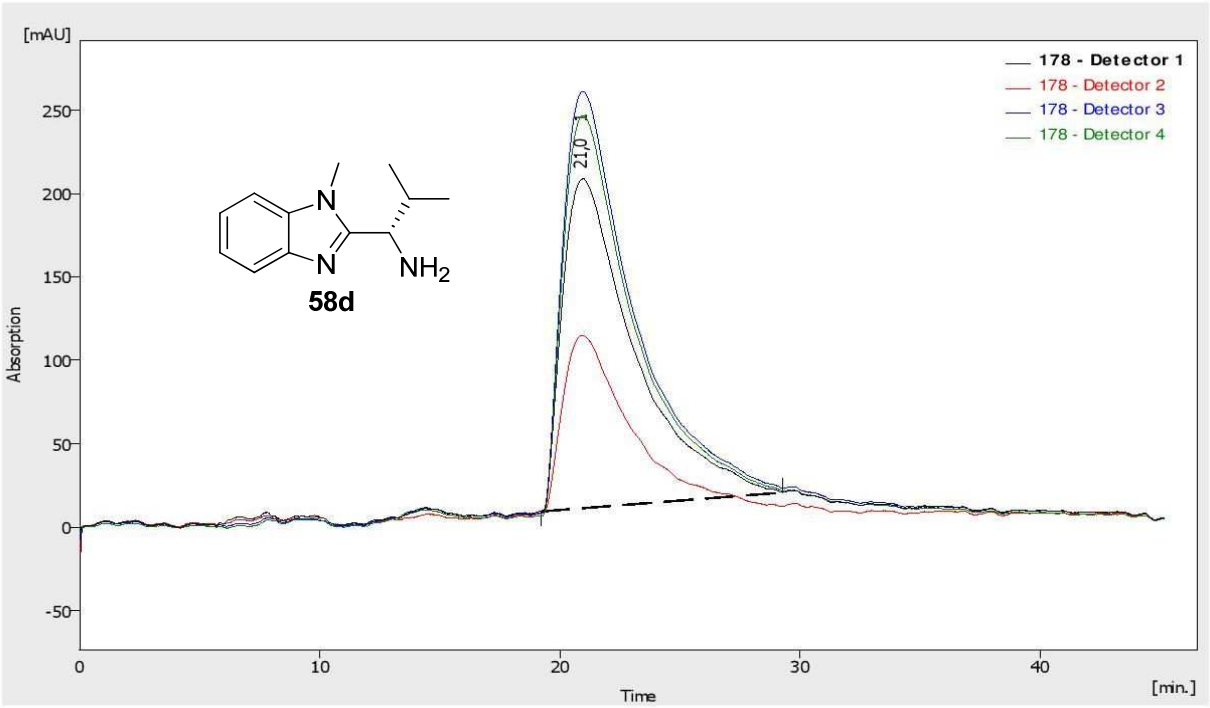
	Reten. Time [min]	Area [mAU.s]	Height [mAU]	Area [%]	Height [%]	W05 [min]	Peak Purity [-]
1	8,042	16391,732	453,577	100,0	100,0	0,53	900
	Total	16391,732	453,577	100,0	100,0		

Attachment 35. *Chiral phase HPLC analysis of* ***58c*** *(Daicel Chiralcel OD-H, n-hexane/i-PrOH 70:30, flow rate 0.8 mL.min^{-1}, t_R = 8.04 min, t_R = 9.65 min). Estimated ee of 99 %.*

Clarity - Chromatography SW
DataApex
www.dataapex.com

Sample Info:

Sample ID	: 2 30/70 IPA/n-hexan 0,5 ml/min	Amount	: 0
Sample	: benzimidazole-Val N-Me deprot	ISTD Amount	: 0
Inj. Volume [mL]	: 20	Dilution	: 1
Method	: benzimidazol-val	By	: Administrator
Description	:		
Created	: 13.6.2016 9:51	Modified	: 13.6.2016 12:28
Column	: Chiralcel OD-H	Detection	:
Mobile Phase	: 20/80 IPA/n-hexan	Temperature	:
Flow Rate	: 0,75 ml/min	Pressure	: 97 bar
Note	:		



Result Table (Uncal - 178 - Detector 1)

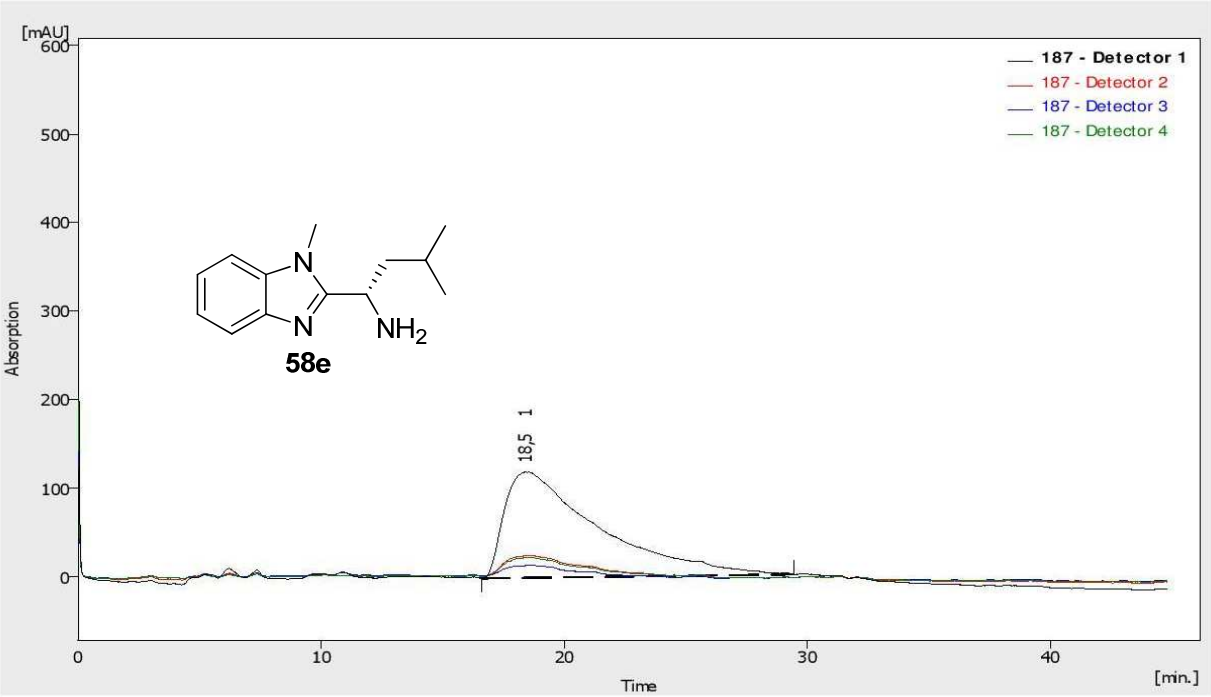
	Reten. Time [min]	Area [mAU.s]	Height [mAU]	Area [%]	Height [%]	W05 [min]	Peak Purity [-]
1	20,975	41409,447	198,099	100,0	100,0	3,02	971
	Total	41409,447	198,099	100,0	100,0		

Attachment 36. *Chiral phase HPLC analysis of* ***58d*** *(Daicel Chiralcel OD-H, n-hexane/i-PrOH 70:30, flow rate 0.8 mL.min^{-1}, t_R = 21.0 min). Estimated ee of 99 %.*

Clarity - Chromatography SW
DataApex
www.dataapex.com

Sample Info:

Sample ID	: 1	Amount	: 0
Sample	: benzimidazol-Leu N-Me deprot.	ISTD Amount	: 0
Inj. Volume [mL]	: 20	Dilution	: 1
Method	: benzimidazol-leu	By	: Administrator
Description	:		
Created	: 13.6.2016 12:33	Modified	: 13.7.2016 13:36
Column	:	Detection	:
Mobile Phase	:	Temperature	:
Flow Rate	:	Pressure	:
Note	:		



Result Table (Uncal - 187 - Detector 1)

	Reten. Time [min]	Area [mAU.s]	Height [mAU]	Area [%]	Height [%]	W05 [min]	Peak Purity [-]
1	18,533	31998,689	119,020	100,0	100,0	3,90	830
	Total	31998,689	119,020	100,0	100,0		

Attachment 37. *Chiral phase HPLC analysis of* ***58e*** *(Daicel Chiralcel OD-H, n-hexane/i-PrOH 70:30, flow rate 0.8 mL.min^{-1}, t_R = 18.5 min). Estimated ee of 99 %.*

Clarity - Chromatography SW
DataApex
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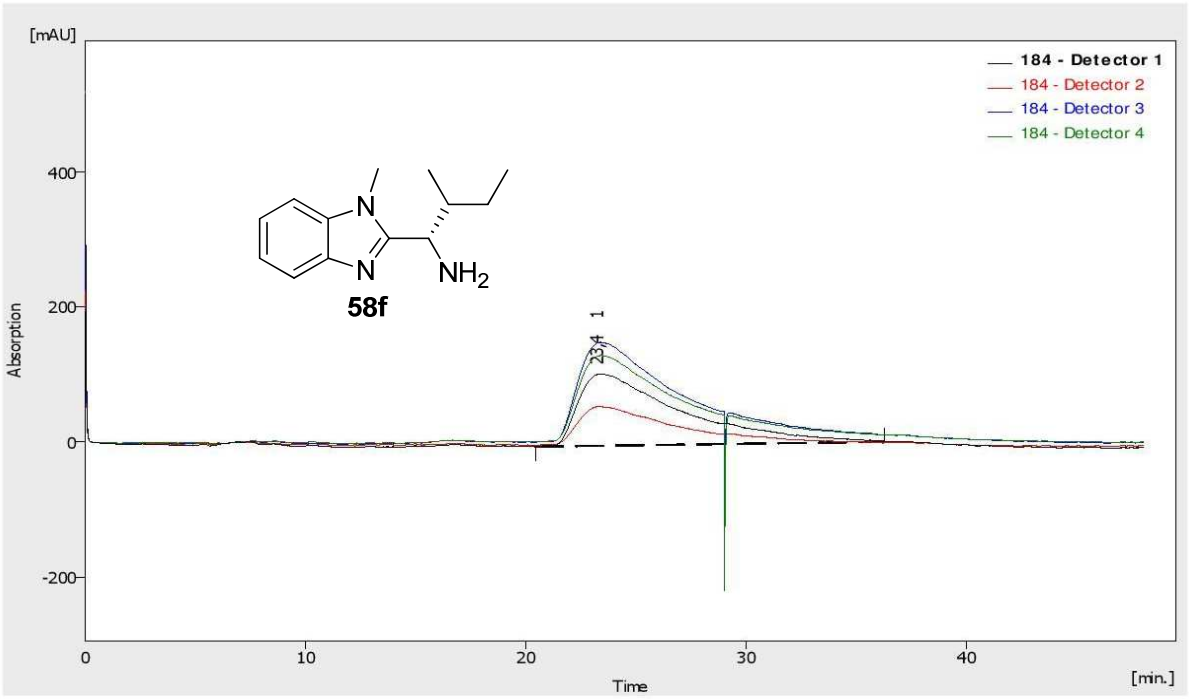
Sample Info:

Sample ID	: pure	Amount	: 0
Sample	: benzimidazol-Ile	ISTD Amount	: 0
Inj. Volume [mL]	: 20	Dilution	: 1
Method	: benzimidazol-Ile	By	: Administrator
Description	:		
Created	: 14.6.2016 13:21	Modified	: 15.6.2016 10:07
Column	: Chiralcel OD-H	Detection	:
Mobile Phase	: 30/70 IPA/n-hexan	Temperature	:
Flow Rate	: 0,5 ml/min	Pressure	: 46 bar
Note	:		



Result Table (Uncal - 184 - Detector 1)

	Reten. Time [min]	Area [mAU.s]	Height [mAU]	Area [%]	Height [%]	W05 [min]	Peak Purity [-]
1	23,358	34533,562	106,192	100,0	100,0	4,65	925
	Total	34533,562	106,192	100,0	100,0		

Attachment 38. *Chiral phase HPLC analysis of* ***58f*** *(Daicel Chiralcel OD-H, n-hexane/i-PrOH 70:30, flow rate 0.8 mL.min^{-1}, t_R = 23.4 min). Estimated ee of 99 %.*

Clarity - Chromatography SW
DataApex
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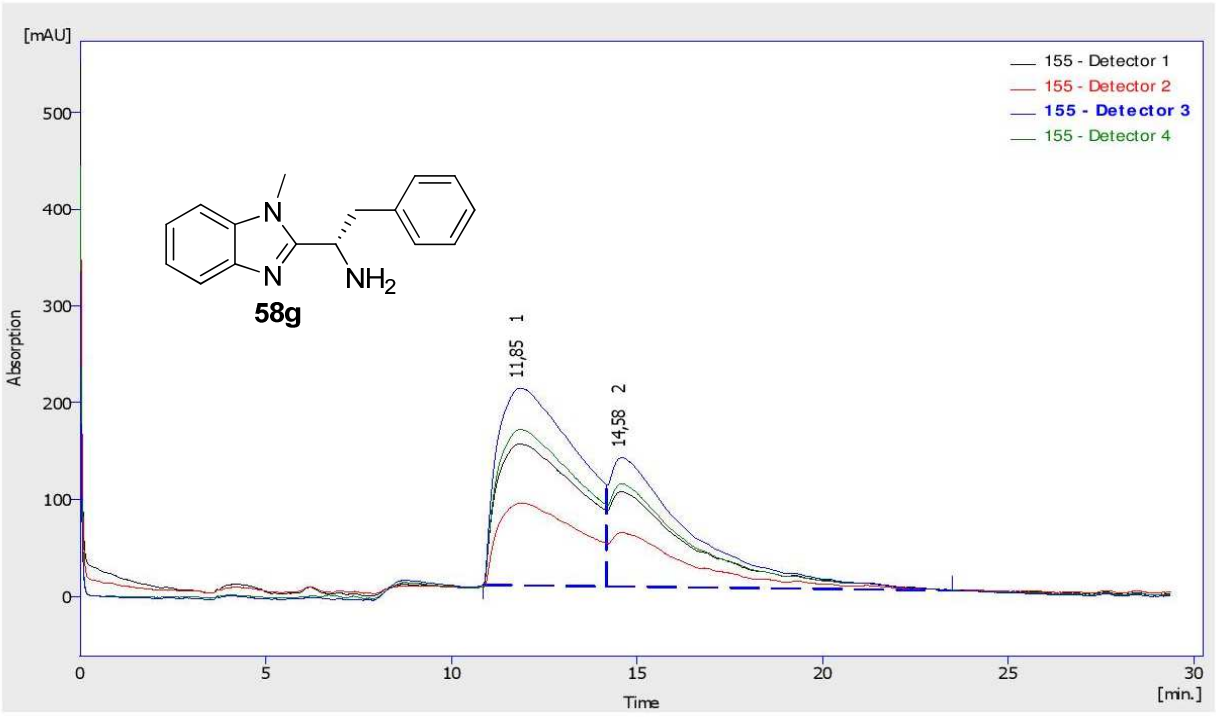
Sample Info:

Sample ID	: 685/15	Amount	: 0
Sample	: Phe-benzimidazole N-CH3 deprotected	ISTD Amount	: 0
Inj. Volume [mL]	: 20	Dilution	: 1
Method	: benzimidazol-Phe	By	: Administrator
Description	: Benzyl derivative		
Created	: 5.12.2014 8:53	Modified	: 23.8.2016 14:23
Column	: AD-H	Detection	:
Mobile Phase	: 10:90 iPrOH:hexane	Temperature	:
Flow Rate	: 0,8 ml/min	Pressure	:
Note	:		



Result Table (Uncal - 155 - Detector 3)

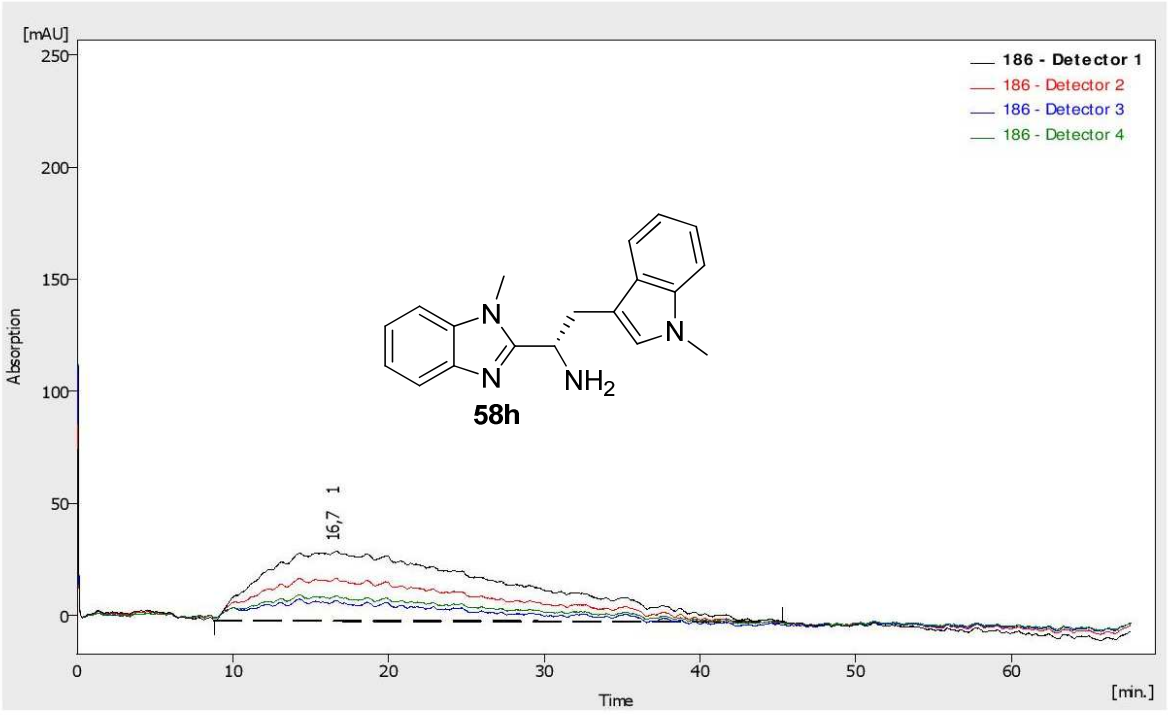
	Reten. Time [min]	Area [mAU.s]	Height [mAU]	Area [%]	Height [%]	W05 [min]	Peak Purity [-]
1	11,850	30348,863	203,409	60,0	60,4	3,08	984
2	14,583	20239,466	133,195	40,0	39,6	1,94	725
	Total	50588,329	336,604	100,0	100,0		

Attachment 39. *Chiral phase HPLC analysis of* ***58g*** *(Daicel Chiralcel OD-H, n-hexane/i-PrOH 90:10, flow rate 0.8 mL.min^{-1}, t_R = 11.8 min, t_R = 14.5 min). Estimated ee of 20 %.*

Clarity - Chromatography SW
DataApex
www.dataapex.com

Sample Info:

Sample ID	: pure	Amount	: 0
Sample	: benzimidazol-Trp	ISTD Amount	: 0
Inj. Volume [mL]	: 20	Dilution	: 1
Method	: benzimidazol-Trp	By	: Administrator
Description	:		
Created	: 14.6.2016 12:26	Modified	: 15.6.2016 12:00
Column	: Chiralcel OD-H	Detection	:
Mobile Phase	: 70/30 n-hexan/IPA	Temperature	:
Flow Rate	: 0,5 ml/min	Pressure	: 46 bar
Note	:		

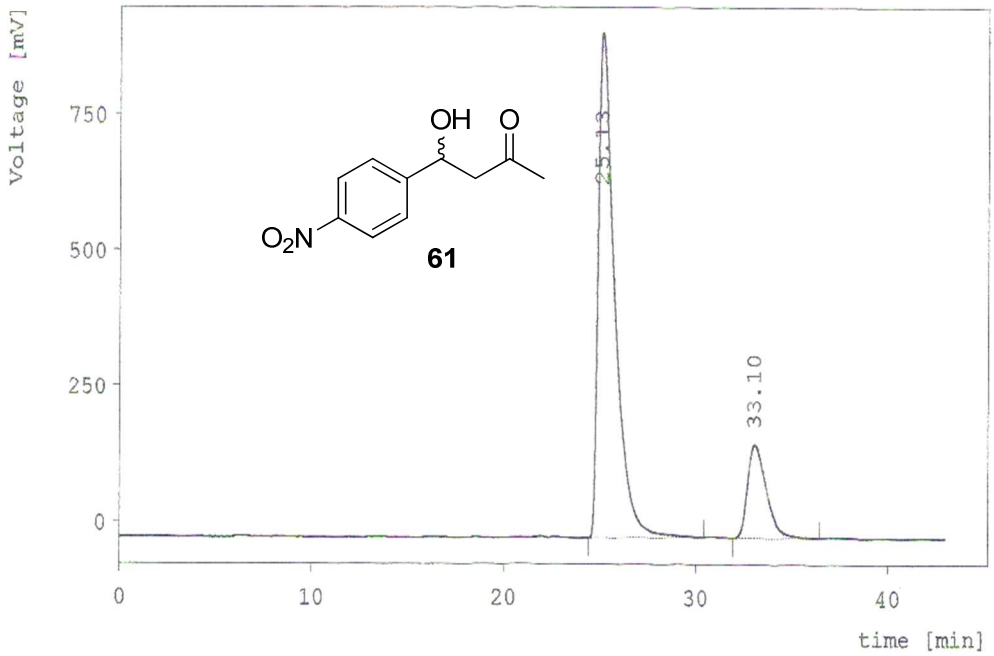


Result Table (Uncal - 186 - Detector 1)

	Reten. Time [min]	Area [mAU.s]	Height [mAU]	Area [%]	Height [%]	W05 [min]	Peak Purity [-]
1	16,658	34046,750	31,084	100,0	100,0	17,56	809
	Total	34046,750	31,084	100,0	100,0		

Attachment 40. *Chiral phase HPLC analysis of* ***58h*** *(Daicel Chiralcel OD-H, n-hexane/i-PrOH 70:30, flow rate 0.8 mL.min^{-1}, t_R = 16.7 min). Estimated ee of 99 %.*

Sample ID	: **PHM001**	Analyst	: **Pavel**
Sample	: **AS-H 70:30**		
Amount	: **5**	Dilution	: **10**
ISTD Amount	: **0**	Inj. Volume	: **20**
From	: **Thu, 28th Mar, 2013 15:57:21**	Printed	: **Thu, 28th Mar, 2013 16:41:03**
Primary	: **prav-13**	Calibration	: **(none)**
Project	: **work1**	Style	: **report**

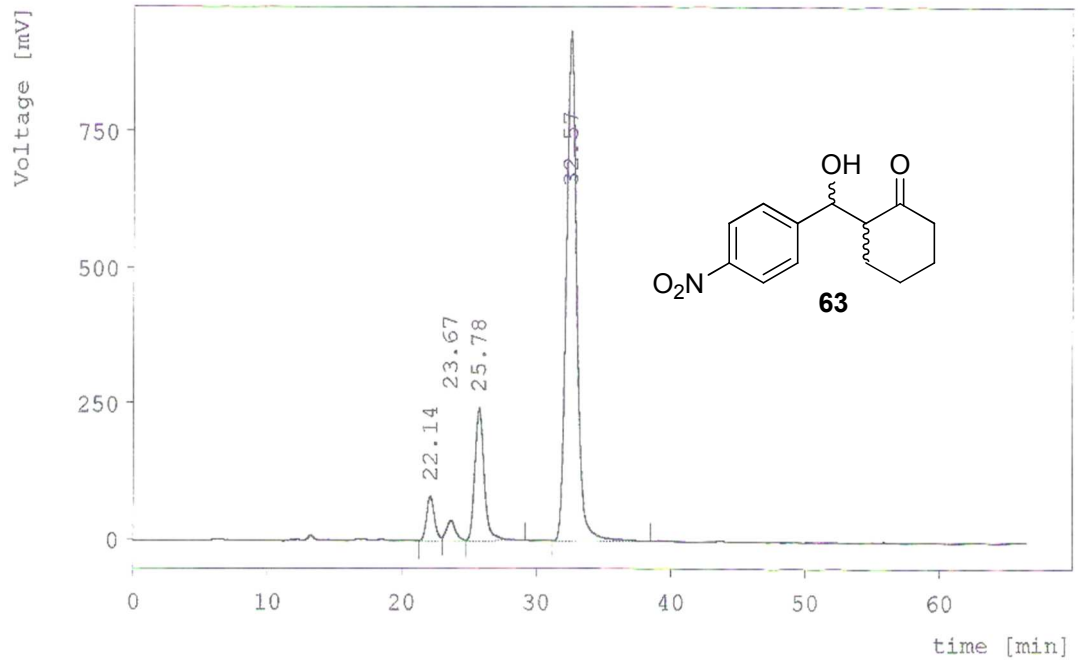


Result Table - Calculation Method Uncal

Peak No.	Reten. time	Area [mV.s]	Height [mV]	W05 [min.]	Area [%]	Height [%]
1	25.133	55767.6525	932.412	0.887	82.917	84.570
2	33.100	11489.5538	170.126	1.033	17.083	15.430
-	Total	67257.2063	1102.538			

Attachment 41. *Chiral phase HPLC analysis of aldol product* ***61*** *(Daicel Chiralpak AS-H, n-hexane/i-PrOH 70:30, flow rate 0.5 mL.min^{-1}, λ = 254 nm, t_R = 25.32 min, t_R = 33.65 min).*

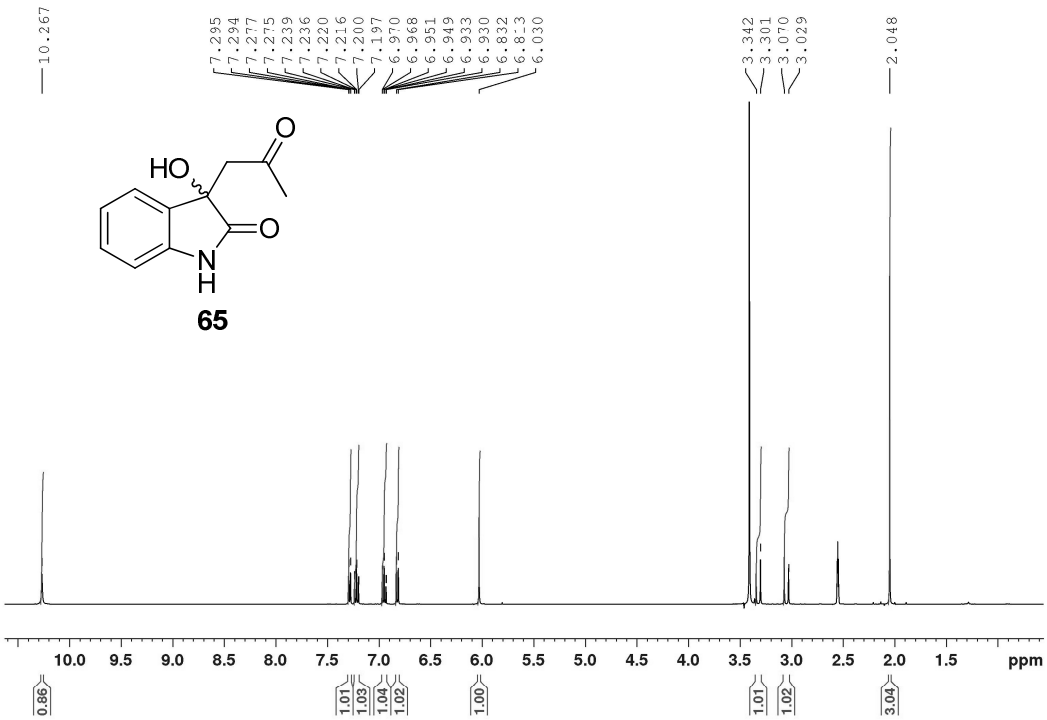
Sample ID	: **P-NO2-6**	Analyst	: **Pavel**
Sample	: **AD-H 20:80**		
Amount	: **5**	Dilution	: **10**
ISTD Amount	: **0**	Inj. Volume	: **20**
From	: **Mon, 4th Nov, 2013 11:54:29**	Printed	: **Mon, 4th Nov, 2013 13:01:18**
Primary	: **prav-45**	Calibration	: **(none)**
Project	: **work1**	Style	: **report**



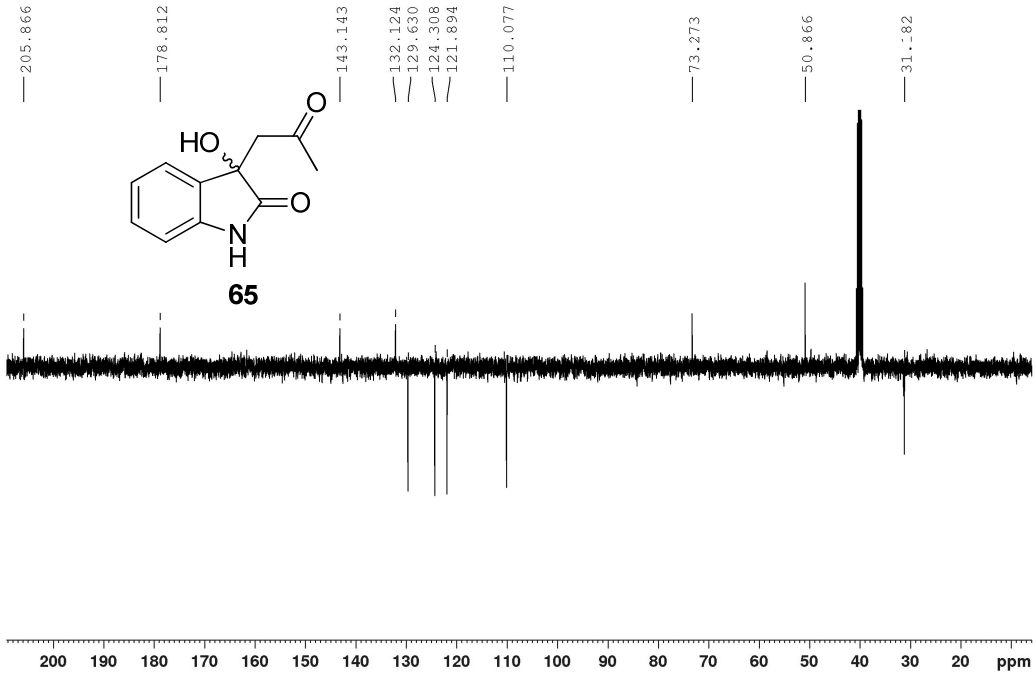
Result Table - Calculation Method Uncal

Peak No.	Reten. time	Area [mV.s]	Height [mV]	W05 [min.]	Area [%]	Height [%]	
1	22.140	3362.4156	80.626	0.653	4.960	6.208	SYN 32%
2	23.667	1733.6106	36.371	0.733	2.557	2.800	
3	25.780	11935.0088	244.491	0.733	17.607	18.825	ANTI 62%
4	32.573	50754.5547	937.238	0.813	74.876	72.167	
-	Total	67785.5897	1298.726				

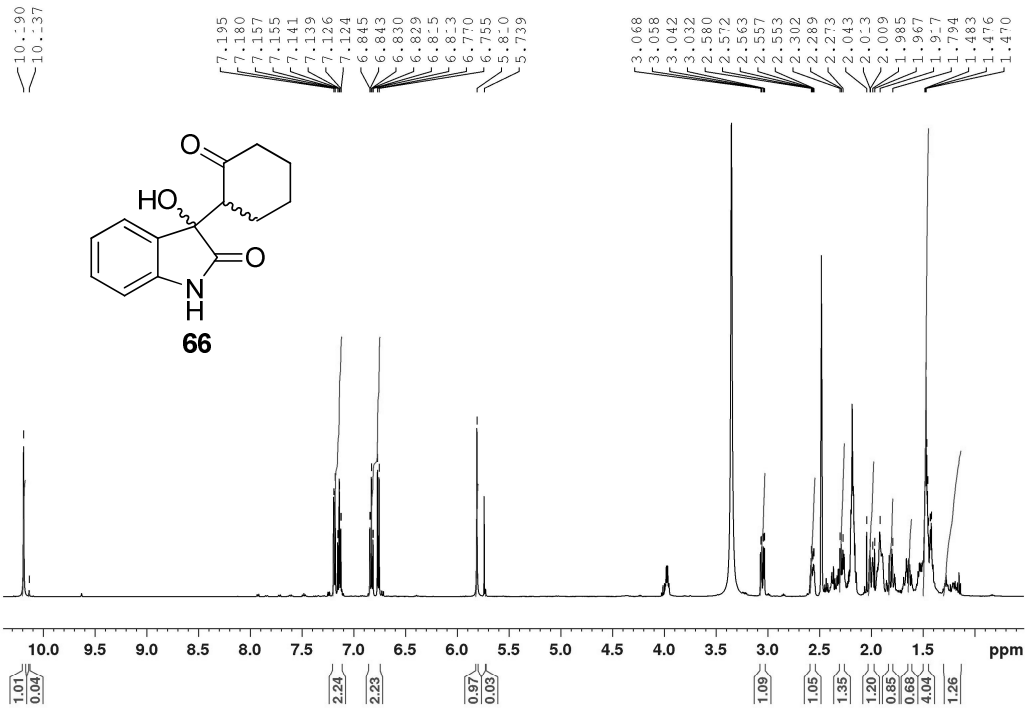
Attachment 42. *Chiral phase HPLC analysis of aldol product* ***63*** *(Daicel Chiralpak AD-H, n-hexane/i-PrOH 80:20, flow rate 0.5 mL.min^{-1}, λ = 254 nm, t_R(syn) = 22.14, t_R(syn) = 23.67, t_R(anti) = 25.78 min, t_R(anti) = 32.57 min).*



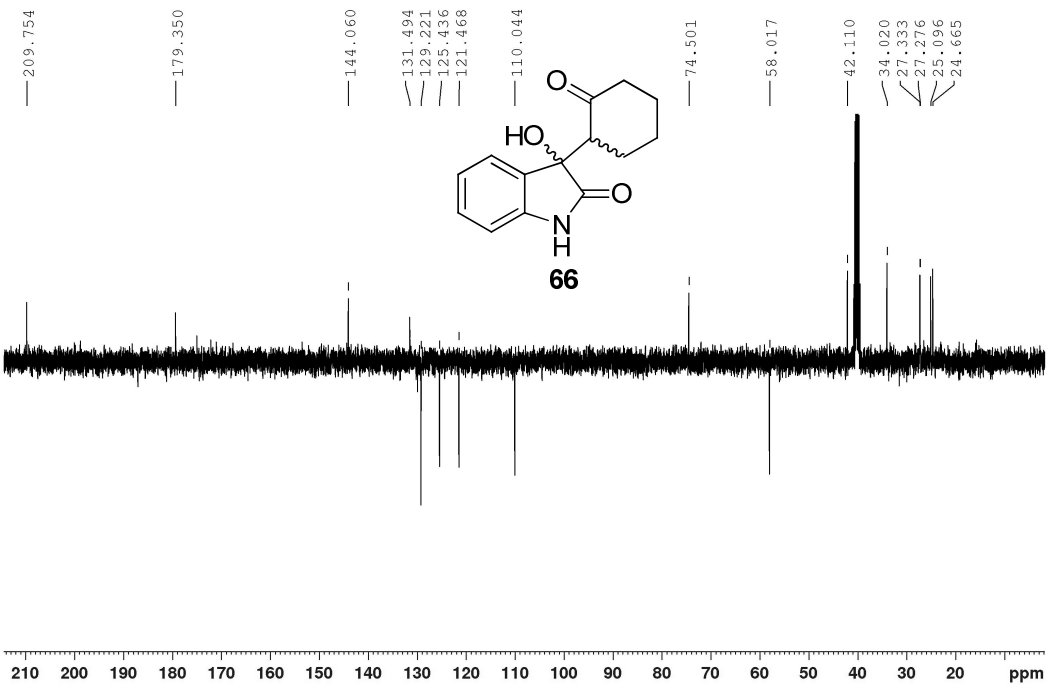
Attachment 43. *^{1}H NMR (DMSO-d_6, 400MHz) spectrum of aldol product **65**.*



Attachment 44. *^{13}C NMR (DMSO-d_6, 100MHz) spectrum of aldol product **65**.*



Attachment 45. *^{1}H NMR (DMSO-d_6, 400MHz) spectrum of aldol product **66**.*



Attachment 46. *^{13}C NMR (DMSO-d_6, 100MHz) spectrum of aldol product **66**.*

Clarity - Chromatography SW
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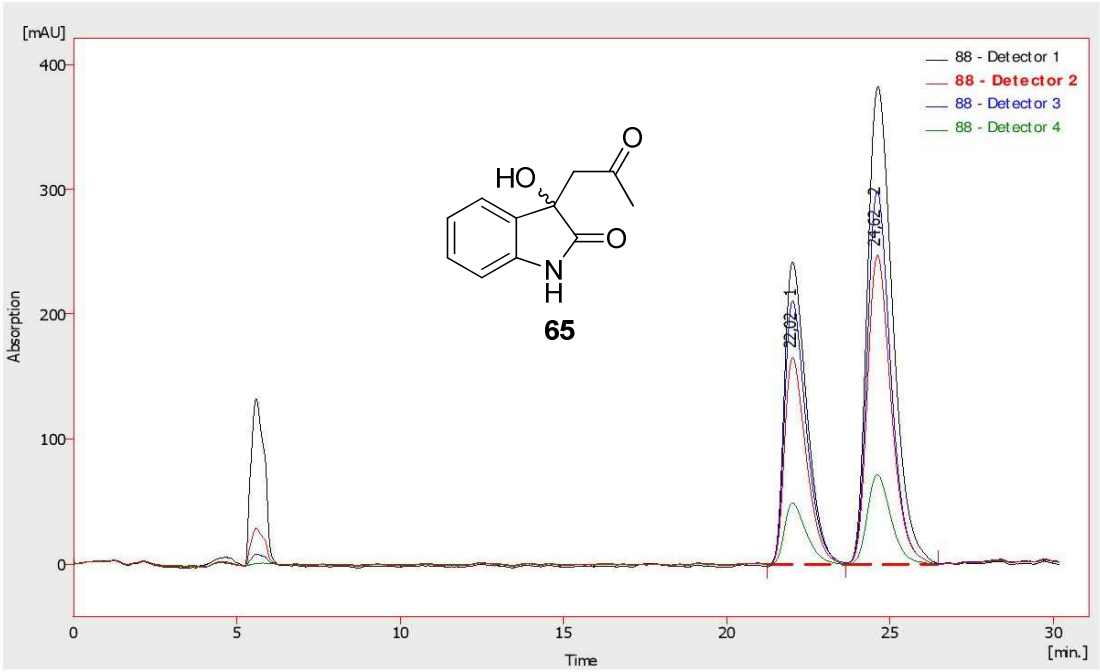
Sample Info:

Sample ID	: 21	Amount	: 0
Sample	: 3-hydroxy-3-(2-oxoprop-1-yl)indole-2-one	ISTD Amount	: 0
Inj. Volume [mL]	: 20	Dilution	: 1
Method	: 3-hydroxy-3-(2-oxoprop-1-yl)inodol-2-on	By	: Administrator
Description	:		
Created	: 27.7.2015 11:22	Modified	: 15.1.2016 12:11
Column	: Chiralcel OJ-H	Detection	:
Mobile Phase	: iPrOH/n-hexan 20/80	Temperature	:
Flow Rate	: 0,8 ml/min	Pressure	: 55 bar
Note	:		



Result Table (Uncal - 88 - Detector 2)

	Reten. Time [min]	Area [mAU.s]	Height [mAU]	Area [%]	Height [%]	W05 [min]	Peak Purity [-]
1	22,017	7657,416	165,289	38,0	40,1	0,72	886
2	24,617	12506,163	246,864	62,0	59,9	0,78	867
	Total	20163,579	412,153	100,0	100,0		

Attachment 47. *Chiral phase HPLC analysis of aldol product* ***65*** *(Daicel Chiralpak OJ-H, n-hexane/i-PrOH 80:20, flow rate 0.8 mL.min^{-1}, λ = 254 nm, t_R = 22.02 min, t_R = 24.62 min).*

Clarity - Chromatography SW
DataApex
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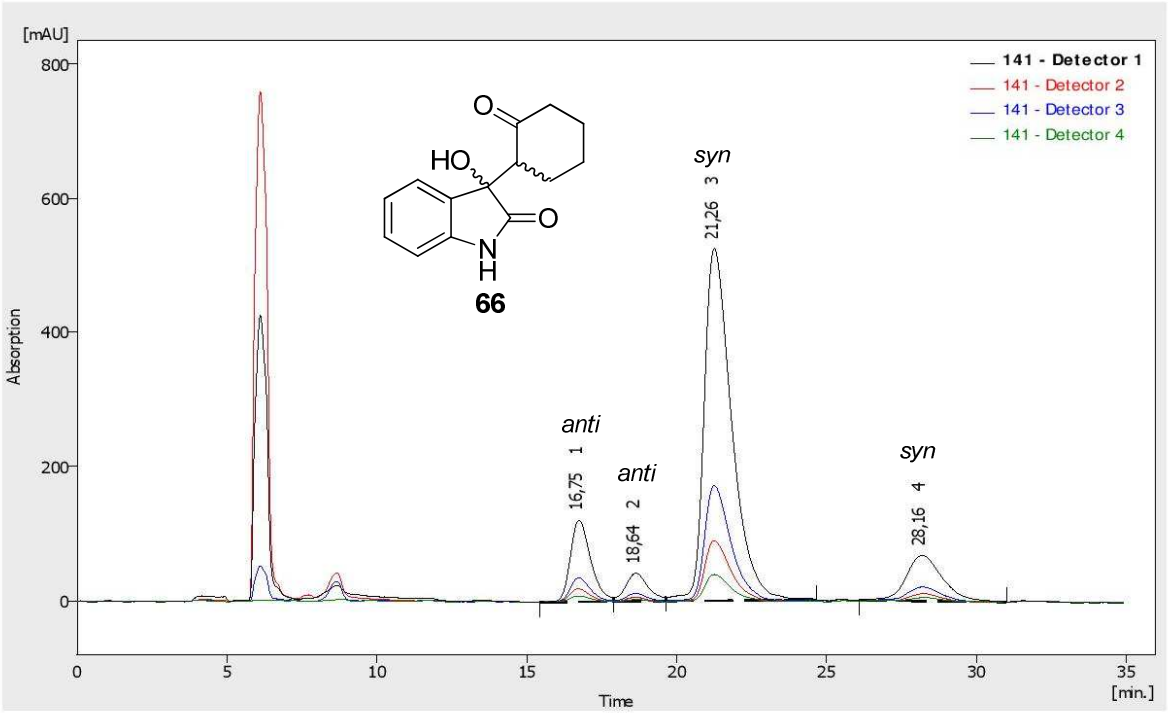
Sample Info:

Sample ID	: 4	Amount	: 0
Sample	: 3-Hydroxy-3-(2-oxocyclohexyl)indolin-2-one	ISTD Amount	: 0
Inj. Volume [mL]	: 20	Dilution	: 1
Method	: 3-Hydroxy-3-(2-oxocyclohexyl)indolin-2-one	By	: Administrator
Description	:		
Created	: 25.2.2016 10:04	Modified	: 18.4.2016 10:25
Column	: Chiralcel OJ-H	Detection	:
Mobile Phase	: 85/15 hexan/iPrOH	Temperature	:
Flow Rate	: 0,8 ml/min	Pressure	:
Note	:		



Result Table (Uncal - 141 - Detector 1)

	Reten. Time [min]	Area [mAU.s]	Height [mAU]	Area [%]	Height [%]	W05 [min]	Peak Purity [-]
1	16,750	5746,576	121,437	12,2	16,1	0,72	633
2	18,642	2196,438	41,908	4,6	5,6	0,78	785
3	21,258	33532,988	523,421	71,0	69,4	0,96	663
4	28,158	5786,443	67,946	12,2	9,0	1,26	601
	Total	47262,445	754,713	100,0	100,0		

Attachment 48. *Chiral phase HPLC analysis of aldol product* ***66*** *(Daicel Chiralpak OJ-H, n-hexane/i-PrOH 85:15, flow rate 0.8 mL.min^{-1}, λ = 254 nm, t_R(anti) = 16.75, t_R(anti) = 18.64, t_R(syn) = 21.25 min, t_R(syn) = 28.16 min).*

ÚDAJE PRO KNIHOVNICKOU DATABÁZI

Název práce	Využití α-aminokyselin v syntéze dusíkatých heterocyklů
Autor práce	Pravinkumar Hansraj Mohite
Obor	Organická chemie
Rok obhajoby	2016
Vedoucí práce	doc. Ing. Filip Bureš, Ph.D.
Anotace	Práce se zaměřuje na zavedení zbytku α-aminokyseliny do struktury pětičlenných dusíkatých heterocyklických sloučenin. Rešeršní část se zaměřila především na deriváty benzo[*d*]imidazolu a benzo[*d*]oxazolu. V experimentální části bylo navrženo a připraveno několik nových derivátů benzo[*d*]imidazolu nesoucích zbytek α-aminokyseliny připojený v poloze C2. Tyto opticky čisté primární aminy byly dále využity jako organokatalyzátory v asymetrických aldolových reakcích.
Klíčová slova	benzo[*d*]imidazol, α-aminokyselina, amin, aldolová reakce, organokatalýza