Development of *ortho*-NosylOXY as a Novel Coupling Reagent for Peptide Synthesis and Related Organic Transformations

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Dedicated

to

My Parents, Uncles & Aunts

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STATEMENT

I do hereby declare that the matter embodied in this thesis is the result of investigations carried out by me in the Department of Chemistry, Indian Institute of Technology Guwahati, India, under the supervision of Dr. Bhubaneswar Mandal.

In keeping with the general practice of reporting scientific observations, due acknowledgements have been made wherever the work described is based on the findings of other investigators.

4th July 2016

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CERTIFICATE

This is to certify that **Mr. Dharm Dev** has been working under my supervision since July 2011 as a regular registered Ph. D. student. I am forwarding his thesis entitled "**Development of *ortho*-NosylOXY as a Novel Coupling Reagent for Peptide Synthesis and Related Organic Transformations**" for being submitted for the Ph. D. (Science) degree from this institute. I certify that he has fulfilled all the requirements according to the rules of this institute regarding the investigations embodied in his thesis and this work has not been submitted elsewhere for a degree.

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Dr. Bhubaneswar Mandal

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Synopsis

The thesis entitled, "Development of *ortho*-NosylOXY as a Novel Coupling Reagent for Peptide Synthesis and Related Organic Transformations", is divided into six chapters along with future directions. The abstracts of the chapters are described below.

Chapter 1: Introduction

Peptides and proteins show the largest structural and functional variation of all the classes of biologically active macromolecules. Biological functions including reproduction, enzyme inhibition, blood pressure regulation, glucose metabolism, thermal control, analgesia and learning and memory are generally thought to be regulated by peptides. They act as hormones, toxins, neuropeptides, receptors, antibiotics, *etc*. Proteins are made up of 'peptides'. Peptides are formed by the condensation of two amino acids through a covalent bond that is known as peptide bond (amide bond). Peptide bonds are the key linkagesin a peptide or protein. Peptide or amide bonds are not limited to the biological systems and are indeed present in most of the major marketed drugs, for examples, Atorvastatin (blocks the production of cholesterol), Lisinopril (inhibitor of angiotensin converting enzyme), Valsartan (blockade of angiotensin-II receptors), and Diltiazem (calcium channel blocker used in the treatment of angina and hypertension).Therefore, formation of peptide bond or amide bond is very important and challenging to the pharmacologists and medicinal chemists. So scientists are finding easier way for peptide and amide syntheses.

Peptide synthesis techniques based on chemical methods are mainly of two types, *i.e.*, *solution phase peptide synthesis* and *solid phase peptide synthesis*. Solution phase peptide synthesis involves mixing of amino acid residues without using any solid support.

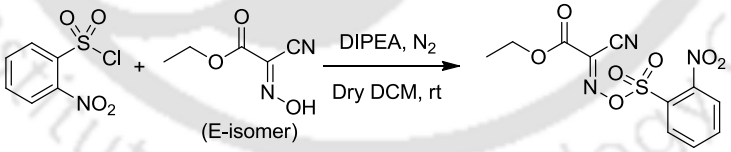
Depending on the requirement, protecting groups are used either at carboxyl end or amine end. Solid phase peptide synthesis (SPPS) is a milestone in the area of peptide synthesis pioneered by Prof. Robert Bruce Merrifield. General principle of SPPS involves: (a) attachment of the first *N*-protected amino acid to resin, (b) *N*-terminal de-protection with the appropriate reagent, (c) coupling of the next amino acid, and (d) Finally cleavage of peptide from the resin.

Numerous coupling reagents have been developed and commercialized including carbodiimides, phosphonium, and uronium/aminium salts. Most of them engage the benzotriazole or azabenzotriazole ring system as an important fragment of their structure, which is subsequently transformed into a good leaving group. After two decades of domination of benzotriazole-based chemistry, with the pioneering work of Albericio *et al.*, a new class of peptide coupling reagents, that is, ethyl 2-cyano-2-(hydroxyimino)-acetate (Oxyma)-based reagents, have been introduced. Oxyma is superior to its counterparts as a racemization suppressant and environmentally friendly reagent. Nevertheless, existing popular coupling reagents still suffer from three major drawbacks. (a) Preparation protocols of these reagents involve harsh conditions and toxic reagents. For example HBTU is synthesized using phosgene (inflammable, causes skin damage) and HOBt (explosive) in carbon tetrachloride, a carcinogenic solvent. Similarly, 1-[(1-(cyano-2-ethoxy-2-oxoethylideneaminooxy) dimethylaminomorpholino-methylene)]-methanaminiumhexafluorophosphate (COMU), an Oxyma-based coupling reagent, is also synthesized using phosgene. (b) Generation of chemical waste for example carcinogenic hexamethylphosphoramide (HMPA) and explosive hydroxybezotriazole (HOBt) are generated as byproducts when benzotriazol-1-yloxytris (dimethylamino)-phosphoniumhexafluorophosphate (BOP) is used as coupling reagent. (c) Furthermore, recycling those reagents may be challenging. Thus, they are not environmentally friendly.

To address the above mentioned drawbacks, we wanted to develop new strategy for peptide synthesis and related organic transformation.

Chapter 2: Ethyl 2-Cyano-2-(2-nitrobenzenesulfonyloxyimino)acetate (*ortho*-NosylOXY): A New Coupling Reagent for Racemization-Free Synthesis of Amide and Peptide

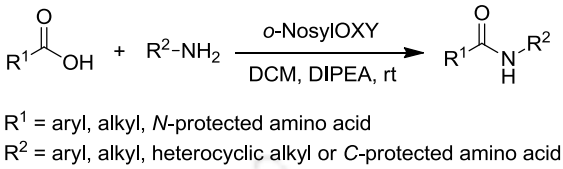
In this chapter we described the development of a new coupling reagent Ethyl 2-Cyano-2-(2-nitrobenzenesulfonyloxyimino)acetate (*ortho*-NosylOXY or *o*-NosylOXY) and its application for the synthesis of amide and peptide. For the synthesis of *o*-NosylOXY, DIPEA was added to a solution of (E)-ethyl-2-cyano-2-(hydroxyimino)acetate (Oxyma) in DCM under nitrogen. The reaction mixture was cooled to 0 °C followed by drop wise addition of *o*-nitrobenzenesulfonyl chloride (*o*-Nosyl-Cl) for 30 min. The reaction mixture was stirred for another 2 h at room temperature (*Scheme 1*). Then the product was recrystallized in hexane and it has been used for the amidation and peptide synthesis as described in this chapter.



Scheme 1. Preparation of reagent *o*-NosylOXY

Amide derivatives are present in most natural products as well as pharmaceutical compounds synthesis of which is important for chemist and industry. To synthesize amides and peptides, here we used newly developed reagent *o*-NosylOXY. Carboxylic acid or *N*-protected amino acid and *o*-NosylOXY dissolved in DCM followed by addition of DIPEA, after 5 min of pre-activation, amine or methyl ester of amino acid (activated

by DIPEA) was added (*Scheme* 2). After completion of the reaction, the product (amide or peptide) was purified with an isolated yield of 78-91%.



Scheme 2. Synthesis of amides and peptides using reagent *o*-NosylOXY

To check the efficiency of *o*-NosylOXY for the synthesis of oligopeptide, we synthesized Boc-Val-Val-IIe-Ala-OMe, the *C*-terminal fragment of the amyloid-β peptide. This is a hydrophobic difficult sequence bearing considerable steric hindrance which is prepared using Boc-chemistry in solution phase.

After obtaining good result for the synthesis of the oligopeptide in solution phase, we wanted to check coupling efficiency of *o*-NosylOXYin solid phase peptide synthesis (SPPS). We have chosen two polypeptide, first hIAPP (22-27) peptide (hIAPP, Human Islet Amyloid Polypeptide: H-Asn-Phe-Gly-Ala-Ile-Leu-Gly-NH_2) and second ACP (65-74) (ACP, Acyl Carrier Protein: H-Val-Gln-Ala-Ala-Ile-Asp-Tyr-Ile-Asn-Gly-NH_2). Both of them are known as difficult sequences for synthesis, since they contain many hydrophobic amino acids and undergo conformational change resulting in aggregation during the synthesis. For the synthesis of hIAPP (22-27) and ACP (65-74), stepwise coupling of constituent amino acids on rink amide MBHA resin using *o*-NosylOXY as a coupling reagent following Fmoc/^{t}Bu orthogonal protection technique based SPPS were used.

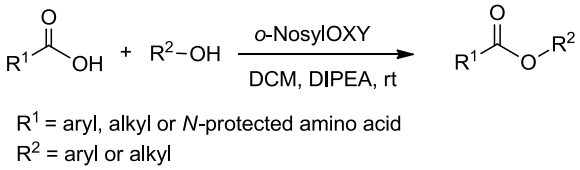
Further, to check the racemization suppression efficiency of *o*-NosylOXY reagent, we prepared a tripeptide, Z-Gly-Phe-Val-OMe, via coupling of Z-Gly-Phe-OH and H-Val-

OMe in solution phase using *o*-NosylOXY, estimated the amount of racemization and compared that with reported data obtained for the synthesis of the same tripeptide using other coupling reagents, such as, HBTU, HATU, HDMB and HDMA. No racemization was observed, when reagent *o*-NosylOXY was used, however, some racemization was noted for other reagents. The racemization study was monitored by parallel HPLC and NMR techniques.

In summary, we have developed a new coupling reagent *o*-NosylOXY, which was easy to prepare, was stable at room temperature and showed an efficient coupling for the racemization free and mild amidation and peptide synthesis. This reagent could be used both in solution and on solid supported resin. Most importantly, the reagent could be recycled and used for further reactions which were very important for green chemistry perspective due to its environment friendly nature.

Chapter 3: Ethyl 2‑Cyano-2-(2-nitrobenzenesulfonyloxyimino)acetate (*o*-NosylOXY): A New Coupling Reagent for Racemization free Synthesis of Ester and Hydroxamate from Carboxylic Acid

In chapter 2, we described the introduction of a new coupling reagent, *o*-NosylOXY and its application for the synthesis of amides and peptides. In this chapter we demonstrated the application of *o*-NosylOXY for the synthesis of esters and hydroxamates. Esterification is a common reaction for organic chemist in academia and indusry. For esterification we took carboxylic acid and *o*-NosylOXY dissolve in DCM followed by addition of DIPEA. After 5 min of pre-activation, alcohol was added. After completion of the reaction, the products were purified, with isolated yield of 82-92% (*Scheme* 3).

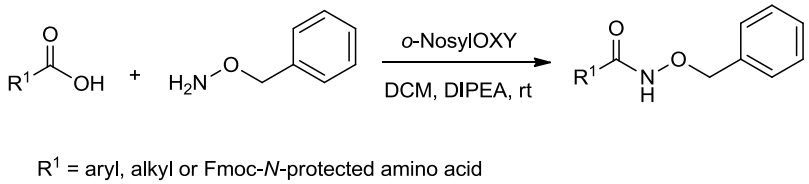


Scheme 3. Synthesis of ester using reagent *o*-NosylOXY

To check the racemization suppression efficiency of reagent *o*-NosylOXY, we prepared two chiral carbon containing esters. We initially synthesized Boc-DL-Phe-OBn and passed through a chiral column in HPLC. Two distinct peaks, corresponding to the two enantiomers, were observed in HPLC chromatogram. Next, we synthesized Boc-L-Phe-OBn following the same strategy. Chromatographic signature of Boc-L-Phe-OBn reveals only one peak corresponding to the enantiopure product. Therefore, it was confirmed that the present protocol does not cause any detectable racemization.

Preparation of Hydroxamate using *o*-NosylOXY

Hydroxamates of amino acids are another interesting class of compounds which possess a broad spectrum of medicinal and biological properties. They are strong metal chelators and show anti-cancer property. For the synthesis of hydroxamates, solution of carboxylic acid or *N*-protected amino acid and *o*-NosylOXY were taken in DCM followed by the addition DIPEA. The reaction mixture was stirred for 3-5 min for pre-activation and the mixture of *O*-benzylhydroxylamine and DIPEA in DCM was added to the reaction mixture (*Scheme* 4).

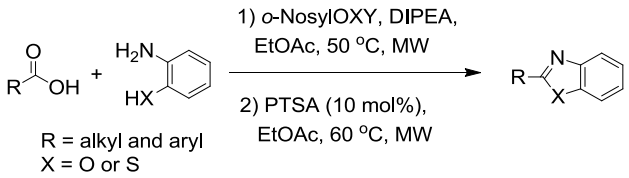


Scheme 4. Synthesis of hydroxamate using reagent *o*-NosylOXY

In conclusion, we have developed a racemization free, simple and mild method for esterification and hydaxamate synthesis from carboxylic acid and *N*-protected amino acid using *o*-NosylOXY.

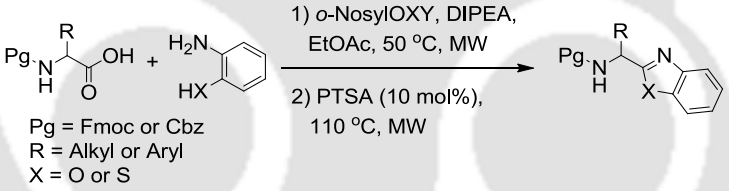
Chapter 4: Benzoxazole and Benzothiazole Synthesis from Carboxylic Acid in Solution and on Resin by Ethyl 2-cyano-2-(2-nitrobenzenesulfonyloxyimino)acetate (*o*-NosylOXY) and *para*-Toluenesulfonic Acid

In previous two chapters we explained the coupling efficiency of reagent *o*-NosylOXY for the synthesis of amides, peptides, esters and hydroxamates. In this chapter we wanted to show the application of the reagent in heterocyclic chemistry, for the synthesis of benzoxazole and benzothiazole of carboxylic acid and *N*-protected amino acid. Benzoxazoles, benzothiazoles, and their derivatives are present in many pharmaceutical important compounds with large spectrum of biological activities. For synthesis of benzoxazole and benzothiozole derivative, we mixed equivalent amount of carboxylic acid, the reagent and DIPEA in ethyl acetate. After 5 min preactivation of the reaction mixture, *o*-aminophenol/*o*-aminothiophenol was added and kept the reaction mixture at 50 °C in MW for 30 min in closed vessel. Then, 10 mol% of *para*-toluene sulfonic acid (PTSA) was added and kept the reaction mixture at 60 °C in MW for another 10 min in closed vessel. After completion of reaction, the products were purified, with isolated yieldof 81-92% (*Scheme* 5).



Scheme 5. Synthesis of benzoxazole and benzothiazole using reagent *o*-NosylOXY

For the synthesis of *N*-protected amino acid based benzoxazole and benzothiazole in solution, we also took equivalent moles of *N*-protected amino acid, reagent and DIPEA mixed in ethyl acetate. After 5 min of pre-activation, *o*-aminophenol or *o*-aminothiophenol was added to the reaction mixture, which was stirred for 30 min at 50 °C in MW (closed vessel). After completion of the first step, PTSA (10 mol%) was added to the reaction mixture, which was heated for another 30-40 min at 110 °C, MW in closed vessel (*Scheme* 6).



Scheme 6. Synthesis of *N*-protected amino acid based benzoxazole and benzothiazole using reagent *o*-NosylOXY

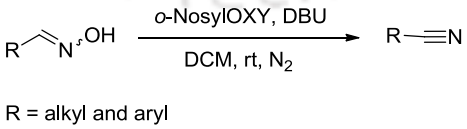
After successful synthesis of *N*-protected amino acid based benzoxazole in solution phase, we also wanted to check the application of this method to the synthesis of benzoxazole on solid supported resin. We synthesized two biologically active benzoxazole derivative $hIAPP_{22\text{-}27}$ (human Islet Amyloid Poly Peptide: H-Asn-Phe-Gly-Ala-Ile-Leu-Gly-NH_2), fragment and fragment of $A\beta_{18\text{-}21}$ (amyloid β, H-Val-Phe-Phe-Ala-Gly-NH_2) peptide. Both are known as difficult sequence for solid phase peptide synthesis

(SPPS). Both of the peptides are synthesized on Rink amide MBHA resin using Fmoc/^{t}Bu based SPPS chemistry.

In conclusion, we developed a method for the synthesis of substituted benzoxazole and benzothiozole using *o*-NosylOXY and catalytic amount of PTSA (10 mol%) under MW in closed vessel. The method is also applied for the synthesis of benzoxazole and benzothiazole derivatives of *N*-protected amino acids in solution phase. Most importantly, synthesis of benzoxazole derivatives of polypeptides via SPPS is also demonstrated.

Chapter 5: Synthesis of Nitrile from Aldoxime in presence of Ethyl 2-cyano-2-(2-nitrobenzenesulfonyloxyimino)acetate (*o*-NosylOXY)

In this chapter we demonstrated the application of the reagent for the synthesis nitrile from aldoxime. Nitriles are important synthons in organic syntheses as they are involved in many functional group transformations. For the synthesis of nitrile, a solution of thealdoxime and *o*-NosylOXY were dissolved in anhydrous DCM, and was placed under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 5 min, and then DBU wasadded drop wise over 2 min. The reaction mixture became a clear homogeneous solution after addition of DBU. The reaction was monitored by TLC (*Scheme* 7). The derivatives of nitrile were synthesized up to 94% yields.

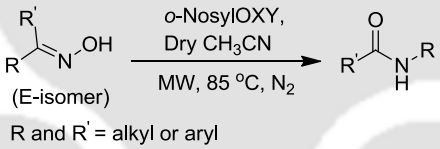


Scheme 7. Synthesis of nitrile from aldoxime using reagent *o*-NosylOXY

In conclusion, we have demonstrated a new method for the synthesis of nitriles from aldoximes under milder conditions using *o*-NosylOXY.

Chapter 6: Synthesis of Amide from Ketoxime via Beckmann Rearrangement using Catalytic amount of Ethyl 2-cyano-2-(2-nitrobenzenesulfonyloxyimino)acetate (*o*-NosylOXY)

Here we have demonstrated the synthesis of amide from ketoxime. The Beckmann rearrangement (BKR) is generally used in organic chemistry to transform ketoximes into amides. It is apowerful method for the synthesis of *ε*-caprolactam. For the synthesis of amide via Beckmann rearrangement, a solution of ketoxime and catalytic amount of *o*-NosylOXY were dissolved in dry acetonitrile at 85 °C under microwave. After completion of reaction, the products were purified, with isolated yield of 69-96% (*Scheme* 8).



Scheme 8. Synthesis of amide from ketoxime using reagent *o*-NosylOXY

We have developed a new highly effective organocatalyst for the Beckmann rearrangement of ketoximes to corresponding amides/lactams with good yields. This finding will broaden the scope of catalytic Beckmann rearrangement.

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Dharm Dev

Abbreviations

Boc	*tert*-Butyloxycarbonyl
BOP	Benzotriazol-1-yloxytris(dimethylamino) phosphonium hexafluorophosphate
Bzl	Benzyl
Cbz	Benzyloxycarbonyl
CDI	*N*, *N*′-carbonyldiimidazole
$CHCl_3$	Chloroform
CH_3CN	Acetonitrile
DCM	Dichloromethane
EDC	1-Ethyl-3-(3-(dimethylamino)propyl)carbodiimide
DABCO	1, 4-Diazabicyclo[2.2.2]octane
DBU	Diazabicyclo[5.4.0]undec-7-ene
DIPEA	Diisopropylethyl amine
DMF	*N*, *N*-dimethyl formamide
DMSO	Dimethyl sulfoxide
ESI MS	Electrospray ionization mass spectrometry
EtOAc	Ethyl acetate
Et_3N	Triethylamine
Fmoc	9-Fluorenylmethoxycarbonyl
FT-IR	Fourier transformation infrared spectroscopy
HATU	*N*-[(dimethylamino)-1*H*-1,2,3-triazolo[4,5-*b*]pyridin-1-yl-methylene)-*N*-methylmethanaminiumhexafluorophosphate-*N*-oxide
HBTU	*N*-[(1*H*-benzotriazol-1-yl)(dimethylamino)methylene]-*N*-methyl methanaminiumhexafluorophosphate-*N*-oxide

HDMA	1-((Dimethylamino)-(morpholino)methylene)-1*H*-[1,2,3]triazolo[4,5-*b*]-pyridiniumhexafluorophosphate-3-oxide
HDMB	1-((Dimethylamino)(morpholino)methylene)-1*H*-benzotriazolium-hexafluorophosphate-3-oxide
HOBt	1-Hydroxy benzotriazole
HPLC	High pressure liquid chromatography
LC-MS	Liquid chromatography mass spectrometry
mM	millimolar
MW	Microwave
mL	milliliter
NMR	Nuclear magnetic resonance
o-NosylOXY	Ethyl 2-Cyano-2-(2-nitrobenzenesulfonyloxyimino)acetate
O^{t}Bu	*tert*-Butyl ester
Oxyma	Ethyl 2-cyano-2-(hydroxyimino)acetate
PTSA	Para-toulenesulphonic acid
p-TsOH	Para-toulenesulphonic acid
PyBOP	Benzotriazole-1-yl-oxy-tris-pyrolidine-phosphoniumhexafluorophosphate
RB	Round bottom flask
RP	Reverse phase
SPPS	Solid phase peptide synthesis
^{t}Bu	*tert*-Butyl
TCT	Trichlorotriazene
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
Z	Benzyloxycarbonyl

Amino Acids

Ala	A	Alanine
Arg	R	Arganine
Asn	N	Asparagine
Asp	D	Aspartic acid
Cys	C	Cysteine
Gln	Q	Glutamine
Glu	E	Glutamic acid
Gly	G	Glycine
His	H	Histidine
Ile	I	Isoleucine
Leu	L	Leucine
Lys	K	Lysine
Met	M	Methionine
Phe	F	Phenylalanine
Pro	P	Proline
Pyl	O	Pyrrolysine
Sec	U	Selenocysteine
Ser	S	Serine
Thr	T	Threonine
Trp	W	Tryptophan
Tyr	Y	Tyrosine
Val	V	Valine

Chapter 1: Introduction

1.1. Introduction

The thesis describes the development of novel methodologies for the synthesis of amides, peptides, esters, hydroxamates and peptide based benzoxazoles, benzothiazoles as well as nitriles using a newly developed efficient coupling reagent. These scaffolds are present in most of the pharmaceutical and biologically active products. The importance, existing methods for synthesis of above cited molecules, and drawbacks associated with the existing traditional methods are introduced briefly in this chapter as.

1.2. Amino acids

Peptides and proteins are important class of bio-macromolecules which play a vital role in the normal functioning of living systems. Proteins act as enzymes, hormones, antibiotics, toxins and receptors, which constitute a major portion of muscle, hair and skin. Amino acids are the smallest building block of peptides and proteins. These amino acids are connected to each other with covalent bond, which is known as peptide (amide) bond, to form peptides and proteins. Proteins are primarily polypeptide chains with usually more than100 amino acid residues and the size may vary from few hundred to several thousand kilo Daltons whereas peptides mostly constructed with 2-50 amino acid residues. There

are 22 standard amino acids that are usually found in proteins, which are also known as coded or proteinogenic amino acids. The coded or α-amino acid has a central chiral carbon which is connected with a carboxylic acid, an amine group, hydrogen and a distinctive R group (*Figure 1.2.1*). R can be a hydrogen atom or alkyl chains bearing acidic, basic, hydrophobic, hydrophilic, redox-active, bulky or compact moieties. Chemical properties of amino acids depend on side chain R. Amino acids without polar groups like Alanine, Valine, Leucine, Isoleucine, Phenyl alanine, Methionine, and Proline, are hydrophobic. Polar group containing amino acids such as Glycine, Serine, Threonine, Cysteine, Selenocysteine, Asparagine, and Glutamine, are hydrophilic. Acidic group containing amino acids are Aspartic acid and Glutamic acid. Basic group containing amino acids are Lysine, Pyrrolysine, Arginine, and Histidine. α-Carbon of all the natural amino acids has L-configuration.

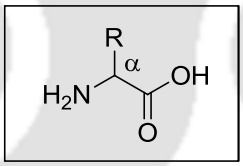


Figure 1.2.1. General structure of an amino acid

1.3. Importance of amides and peptides, esters, benzoxazoles, benzothiazoles and nitriles

1.3.1. Importance of amides and peptides

The amide (peptide) bond is certainly one of the most important parts in chemistry. Making up of peptide bonds in proteins such as enzymes, hormones are essential to sustain life, and it is also one of the most prolific moieties in pharmaceutical molecules,

agrochemicals and natural products. For example, Lidocaine[1] (*Figure 1.3.1.1*), a medicine belongs from local anesthetics in the family of medicines, used as an antiarrhythmia agent. This medicine prevents pain by blocking the signals at the nerve endings in the skin. Atorvastatin[2] (*Figure 1.3.1.1*) is the top selling drug worldwide since 2003, a calcium salt under the trade name Lipitor®, a member of the drug class known as statins and block the production of cholesterol. It prevents strokes through anti-inflammatory activity. Lisinopril[3] (*Figure 1.3.1.1*) is belongs to a class of medications called angiotensin-converting enzyme (ACE) inhibitors. It is used for the treatment of high blood pressure and heart failure. It has also earned a significant place in medicine as Prinivil and Zestril. Similarly, Imatinib[4] (*Figure 1.3.1.1*) is a tyrosine-kinase inhibitor. It is used for the treatment of certain types of cancer such as acute lymphoblastic leukemia and chronic myeloid leukemia.

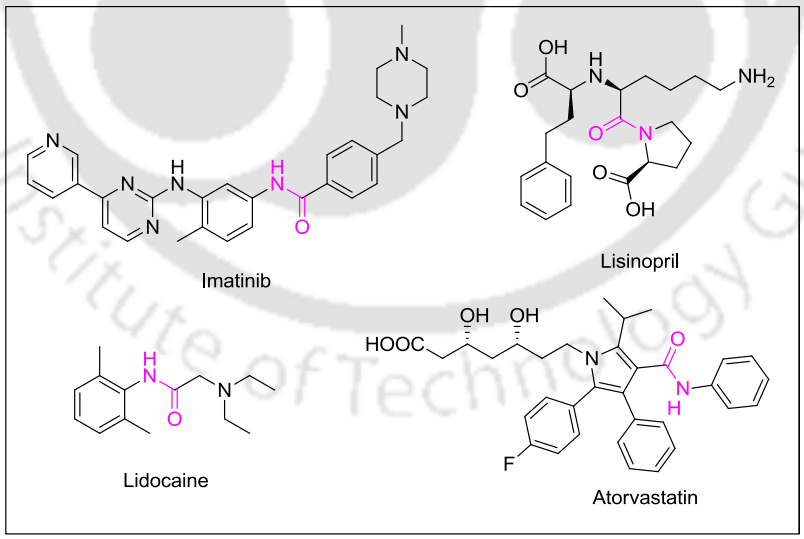


Figure 1.3.1.1. Biologically active amides

Peptides are involved in a variety of physiological and pathological processes and play important roles in modulating various cell functions. Peptide drugs have been successfully applied in treating certain human diseases. For instance, Cyclosporin A

(CyA)[5] (*Figure 1.3.1.2*) was discovered by Borel in 1972, is a powerful immunosuppressive agent, lack of myelotoxicity makes it unique among nonsteroidal drug currently given for immunosuppression. CyA is used as a mainstay of therapy in all types of solid organ transplantation. It also has clinical application in the treatment of autoimmune disorders. Similarly, Goserelin[6] (*Figure 1.3.1.2*) is a luteinizing hormone releasing hormone (LHRH) agonist, is a synthetic analog of LHRH. It is used for treatment of breast cancers and a certain uterus disorder. The peptide, KLVFF[7] (*Figure 1.3.1.2*), can bind full-length Aβ-peptide and arrest its assembly into amyloid fibrils.

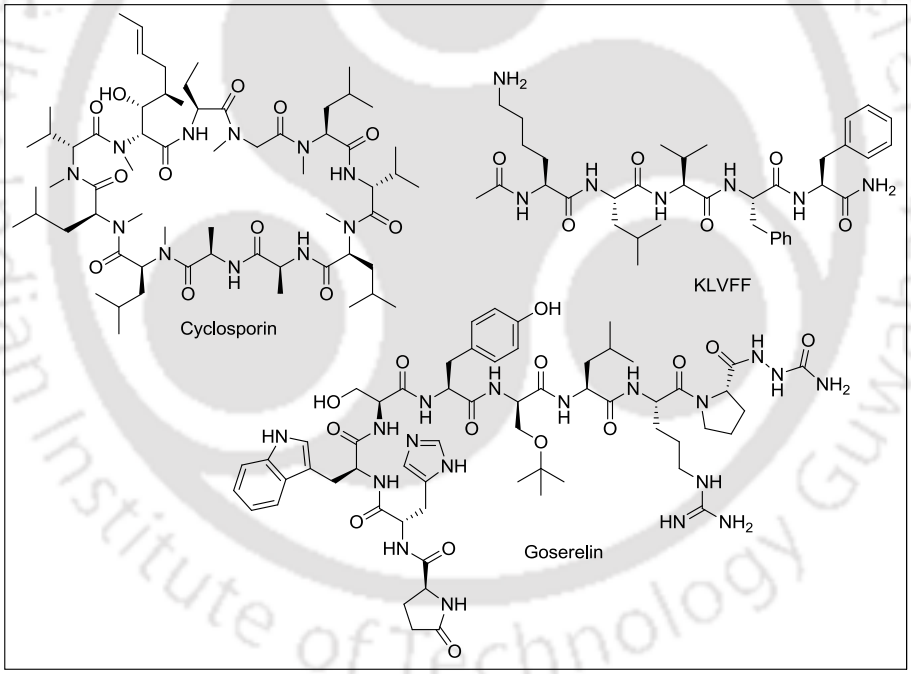


Figure 1.3.1.2. Biologically active peptides

1.3.2. Importance of esters and hydroxamates

No doubt ester bond are present in many biologically active molecules and medicinal compounds. For example, Beclometasone dipropionate[8] (*Figure 1.3.2.1*) is a type of steroid based medicine, which is sold in market with brand name Qvar. It is used for asthma, dermatitis, psoriasis, allergic rhinitis and nasal polyps. Menthyl isovalerate[9] (*Figure 1.3.2.1*) is a main active component of the spasmolytic medicine validolum. It is a drug and sells in market with trade name Validol®. It has a sedative effect on the nervous system and a moderate reflex vaso-dilating effect. Procaine[10-11] (*Figure 1.3.2.1*) is a local anesthetic, which is sold in market with trade name Novocain®. It is used as an injection during surgery and other medical and dental procedures. Its action is completely reversible. Aspirin[12] (*Figure 1.3.2.1*) used for the treatment of in the treatment of a number of conditions, including fever, pain, rheumatic fever, and inflammatory diseases, such as rheumatoid arthritis, pericarditis, and Kawasaki disease. Aspirin's ability to suppress the production of prostaglandins and thromboxane is due to its irreversible inactivation of the cyclooxygenage. Similarly, phorbol[13] ester is a tetracyclic diterpenoid ester. It is a potent tumor-promoting agent and it can be used as an effective biopesticide and insecticide.

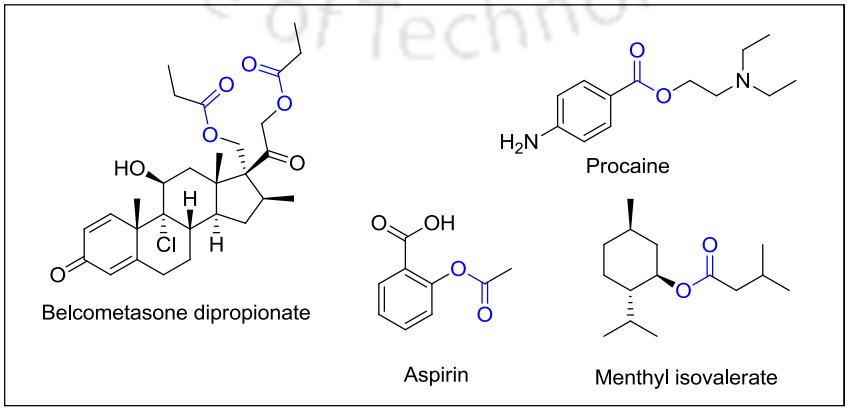


Figure 1.3.2.1. Biologically active esters

Hydroxamic acids have a wide range of biological activities and they are powerful metal ion chelators. For example, Actinonin[14] (*Figure 1.3.2.2*) is first reported potent peptide deformylase (PDF) inhibitor, a naturally occurring antibacterial agent. It was first obtained from the culture filtrates of a *Streptomyces* species. It shows antitumor activity and inhibitor of several metallo hydrolases. It is very potent inhibitors of metallo enzymes and especially matrix metalloproteases. Actinonin also shows active against Gram positive bacteria. Bisucaberin[15] (*Figure 1.3.2.2*) is a 22-membered microbial macrocyclic dihydroxamate siderophore isolated from *Vibrio salmonicida*, an important pathogen of Atlantic salmon (Salmo salar). It has been known to slow tumor cell growth by withholding cellular Fe^{3+} and promoting macrophage mediated cell cytolysis.[16] Similarly, Oxamflatin[17] is an antitumor compound, found to be an inhibitor of mammalian histone deacetylase.

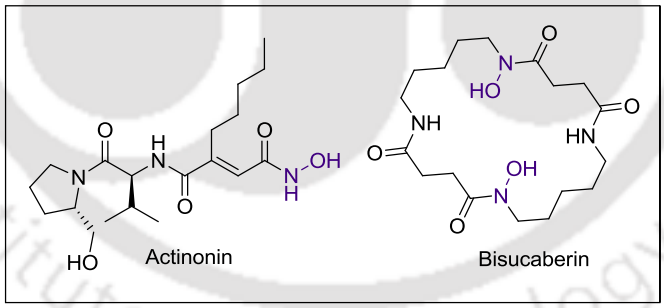


Figure 1.3.2.2. Biologically active hydroxamates

1.3.3. Importance of benzoxazoles and benzothiazoles

Benzoxazoles, benzothiazoles, and their derivatives are important class of heterocyclic compound which have important medicinal and biological activities. They have structural feature in a diverse range of natural products and synthetic drug molecules with wide

range of applications. Benzoxazole scaffold is found in a range of cytotoxic naturally occurring compounds, such as anti-mycobacterial Ileabethoxazole[18] is a novel benzoxazole containing alkaloid, salvianen,[19] Nakijinol B,[20] and AJI9561[21] (*Figure 1.3.3.1*). Some more example of benzoxazole and benzothiazole in medicinal chemistry include, L 695, 697[22] (*Figure 1.3.3.1*), which is a pyridinone non-nucleoside reverse transcriptase inhibitor. It has significant dose activity against HIV-1. PMX 610[23] (*Figure 1.3.3.1*) has been shown to exhibit exquisitely potent (GI50, 0.1 nM) and selective in vitro antitumor properties in human cancer cell lines (e.g., colon, non-small-cell lung and breast subpanels). ERB-041[24] (*Figure 1.3.3.1*) is selective estrogen receptor-β agonists with activity in rodent models of rheumatoid arthritis and endometriosis. Similarly, AMG 517[25] (*Figure 1.3.3.1*) is a potential vanilloid-1 (TRPV1) antagonist.

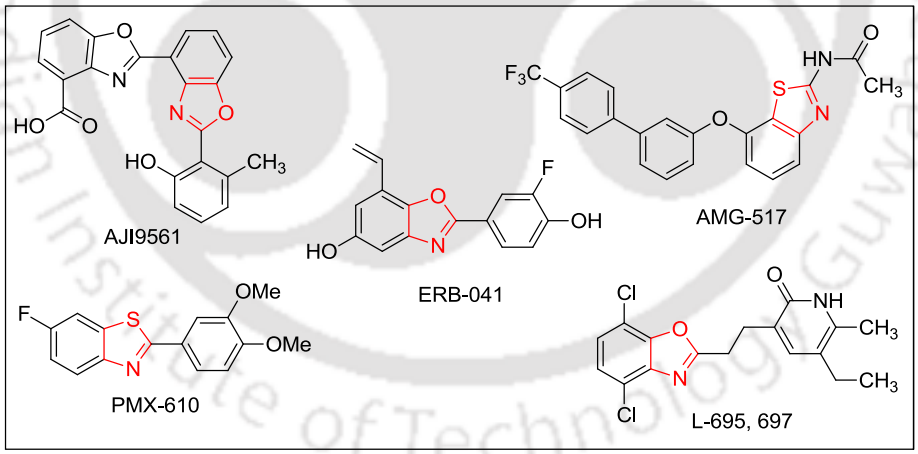


Figure 1.3.3.1. Biologically active substituted benzoxazoles and benzothiazoles

1.3.4. Importance of nitriles

Organonitriles (Aryl nitriles) are an important part of pharmaceuticals, agrochemicals, many natural products, herbicides, pigments, and dyes.[26] In addition; the nitrile moiety

also serves as a key intermediate for a broad range of functional group transformations leading to the formation of amines, aldehydes, carboxylic acids, ketones, amides, and heterocycles.[27] Some important drug which contain nitrile moiety, for example, Fadrozole[28] (*Figure 1.3.4.1*) hydrochloric acid salt, under the trade name Arensin®, is used as a antineoplastic non-steroidal. It is a very potent inhibitor which effectively inhibits aromatase. Verapamil[29] (*Figure 1.3.4.1*) is a class of medications of calcium-channel blocker. It is used for the treatment of high blood pressure and angina. Similarly, Latrozole[30] (*Figure 1.3.4.1*) is also used as an antineoplastic and aromatase inhibitor.

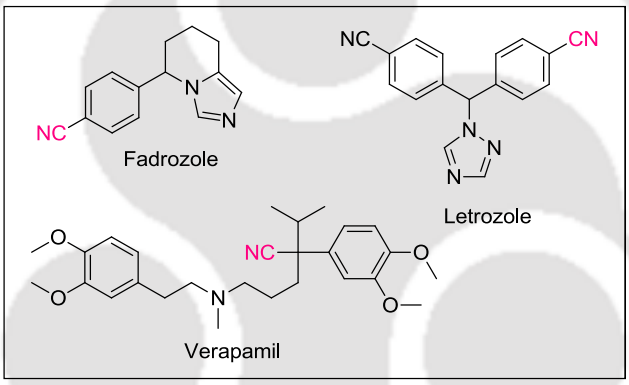
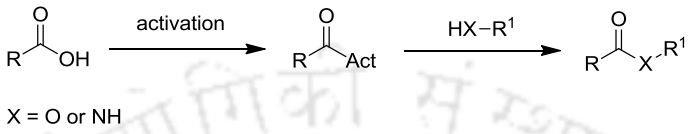


Figure 1.3.4.1. Biologically active nitriles

1.4. Existing methods for the synthesis of amides, esters and peptides

Amide or ester bond formation is a condensation reaction between a carboxylic acid and an amine or alcohol, respectively. Amide bonds are typically synthesized from the combination of carboxylic acids and amines. However, the combination of these two functional groups does not occur spontaneously at ambient temperature. The necessary elimination of water only takes place at high temperature (160-180 °C)[31] conditions typically detrimental to the integrity of the substrates containing common protecting groups, such as Boc, Fmoc, and Cbz. Therefore, first activation of carboxylic group is

necessary (*Scheme 1.4.1*). In order to activate carboxylic acids, one can use so-called coupling reagents, such as acid chlorides, carbonic anhydrides, active esters, phosphonium salt and uronium salt.[32]



Scheme 1.4.1. Principle of the activation process for amide-bond/ester bond formation

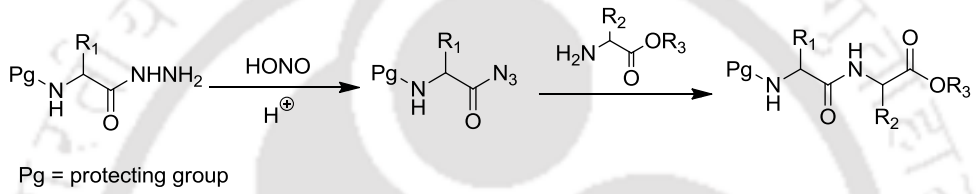
The process usually requires activation of a carboxylic acid moiety in presence of coupling reagents. Activation is the process of replacement of the hydroxyl group of the carboxylic acid with a leaving group as the carboxylic acid would otherwise simply form salts with the amine. The reaction of the activated intermediate and the amine is known as the coupling reaction and the activators are coupling reagents.

The peptide synthesis techniques based on chemical methods are mainly of two types, *i.e., solution phase peptide synthesis* and *solid phase peptide synthesis*.

1.4.1. Solution phase peptide synthesis

Small peptides are usually prepared in solution phase. However, solution phase synthesis of oligo and polypeptides has been largely replaced by solid phase synthesis, introduced by R. B. Merrifield 1963,[33] and taking advantage of the fact that the insolubility of polymers (resin) allows purification by filtration. Solution phase peptide synthesis involves mixing of amino acid residues without using polymer (resin).

In 1881, Curtius developed the first chemical synthesis of a dipeptide.[34] In curtius method, first preparation of acyl azide from acyl hydrazide by the reaction of sodium nitrite with aqueous acetic acid or hydrochloric acid. Acyl azide reacts with the next amino acid in basic medium to form dipeptide (*Scheme 1.4.1.1*). However, the first published synthetic dipeptide, glycylglycin, was synthesized by Emil Fischer in 1901, by hydrolysis of the glycine diketopiperazine and is considered the beginning of peptide chemistry.[35]

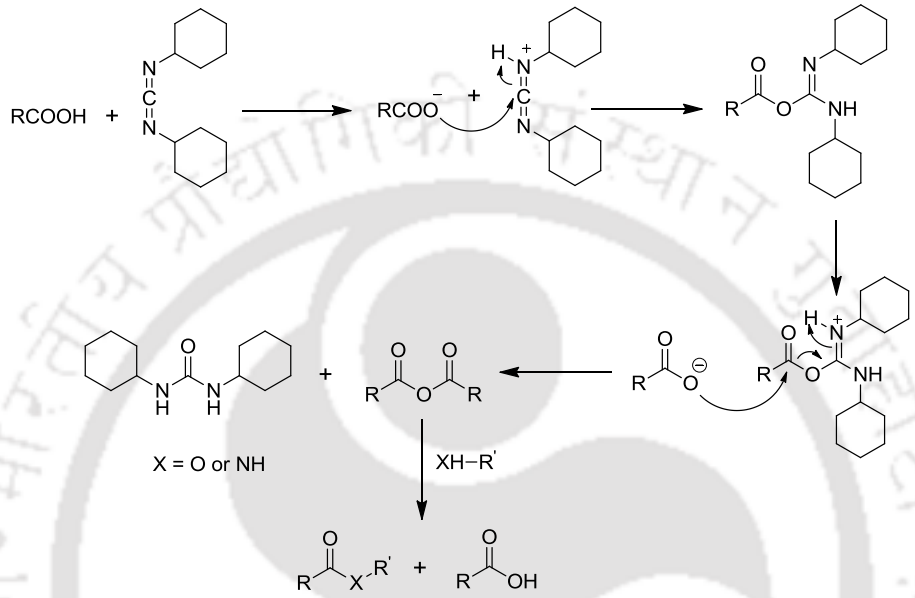


Scheme 1.4.1.1. Curtius approach of peptide synthesis

1.4.1.1. Synthesis of amides, esters, and peptides via anhydrides

Carboxylic acid anhydrides are highly reactive species those readily react with different nucleophiles, such as alcohols, thiols, and amines to form esters, thioesters, and amides, respectively. This strategy ranges from the use of simple symmetric anhydrides to rather refined mixed anhydrides. The process of coupling of individual amino acids can be accomplished through employment of the carbodiimide,[36] 1-ethoxycarbonyl-1,2-dihydroquinoline (EDDQ),[37] cyclic anhydrides (*N*-carboxy anhydrides or Leuch's anhydrides),[38] urethane-protected *N*-carboxy anhydrides (UNCAs).[39] The carbodiimide based method involves coupling *N*- and *C*-protected amino acids by dicyclohexyl-carbodiimide (DCC) as the coupling reagent. Essentially, this coupling reagent promotes dehydration between the free carboxyl group of an *N*-protected amino acid and the free amino group of the *C*-protected amino acid, resulting in the formation of an amide bond

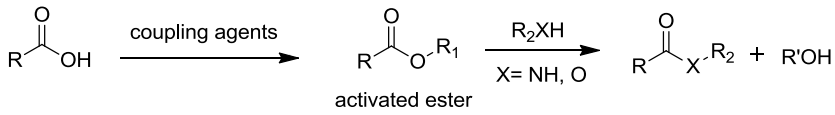
with precipitation of the byproduct, *N*,*N*'-dicylcohexylurea (DCU) (*Scheme 1.4.1.1.1*). This method, however, is hampered by the side reactions which can result in racemization, the formation of (4*H*)-oxazolones and *N*-acylureas.



Scheme 1.4.1.1.1. Preparation of amide and ester via activate ester using DCC

1.4.1.2. Synthesis of amides, esters, and peptides via active esters

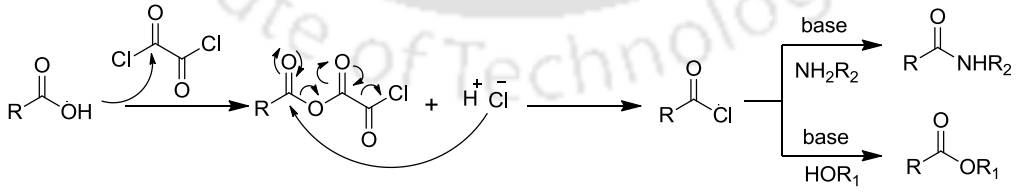
Aryl esters are usually easier to hydrolyse than alkyl esters and are prone to react with a variety of nucleophiles. More importantly, they react with amines or alcohols under mild conditions with usually reduced racemization. In scheme 1.4.1.2.1, we have shown the general reaction of activated ester such as 1-hydroxybenzotriazole (HOBt) ester,[40] 1-hydroxy-7-azabenzotriazole (HOAt) ester,[41] *p*-nitrophenolic ester[42] pentafluorophenolic ester,[43] *N*-hydroxysuccinimide (HOSu),[44] *N*-hydroxy-5-norbornene-endo-2,3-dicarboxyimide (HONB) ester,[45] 2, 4, 5-trichlorophenolic ester,[46] and 2 3-hydroxy-4-oxo-3,4-dihydro-1,2,3-benzotriazine ester,[47] a selection of different alcohols that are commonly used.



Scheme 1.4.1.2.1. Synthesis of amide and ester through activated ester

1.4.1.3. Synthesis of amides, esters, and peptides via acid halides

Using acid halides are one of the easiest methods to activate carboxylic acid for the synthesis of peptide. This is usually a two-step process, first the conversion of the carboxylic acid into the carboxylic acid halide followed by the coupling. There are numerous commercially available acylating agents for the activation of carboxylic acid function into carboxylic acid halide to form amide/ester with amine/alcohol such as pivaloyl chloride,[48] thionyl chloride,[49] oxalyl chloride,[50] phosphorus trichloride,[51] phosphorus pentachloride,[52] phthaloyl dichloride,[53] and cyanuric chloride.[54] The mechanism of acid chloride formation from carboxylic acid using thionyl chloride is illustrated in scheme 1.4.1.3.1. However, acyl chlorides have limited application in peptide coupling because of the danger of hydrolysis, racemisation, cleavage of protecting groups and other side reactions.



Scheme 1.4.1.3.1. Mechanism for acyl chloride formation using oxalyl chloride

1.4.1.4. Synthesis of amides, esters, and peptides using coupling reagents

Using of coupling reagents for the synthesis of amide, ester or peptide directly from carboxylic acid has been accepted as worthy methods till date in comparison with other well-known methods including, anhydride and acid chloride methods. Numerous advantages of using coupling reagents are, easy to perform, control racemization, mild reaction condition, *etc*. In literature various types of coupling reagents available, which are mostly divided into three types, carbodiimides, phosphonium salt and uronium salt based. The carbodiimide based reagents were known as the first developed peptide coupling reagents since 1955 and still in use till date. In this family of coupling reagents, dicyclohexylcarbodiimide (DCC),[36] diisopropylcarbodiimide (DIC)[55] and *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodimide (EDC)[55] are most common (*Figure 1.4.1.4.1*). DCC is mostly applied in solution phase peptide synthesis, in combination with additives such as HOBt or HOSu in order to reduce epimerization in the case of peptides.

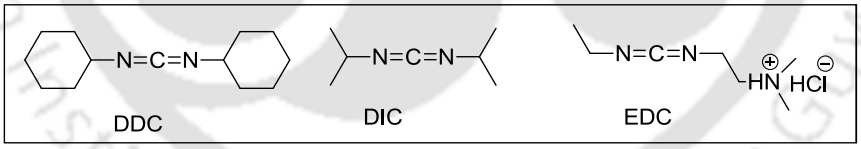


Figure 1.4.1.4.1. Carbodiimide based coupling reagent

Coste and coworkers have developed first HOBt based phosphonium salt type coupling reagent benzotriazol-1-yloxy)tris(dimethylamino)phosphoniumhexafluoro phosphate (BOP),[56] also called Castro's reagent. BOP (*Figure 1.4.1.4.2*) is an excellent coupling reagent with respect to yield and racemization suppression. However, its severe drawback is the toxicity problem due to the carcinogenic hexamethylphosphoramide (HMPA) formed as byproduct during the reaction. In order to prevent the generation of the

undesirable toxic byproduct HMPA, chlorotri(pyrrolidino)phosphoniumhexa-fluorophosphate (PyCloP),[57] bromotri(pyrrolidino) phosphonium hexafluorophosphate (PyBroP)[57], and bromotri-(pyrrolidino) phosphonium hexafluorophosphate (PyBOP)[58] (*Figure 1.4.1.4.2*) was developed by replacing the dimethylamine moiety with pyrrolidine. HOAt based phosphonium salt type coupling reagents, such as (7-aza-benzotriazol-1-yloxy)tris-(dimethylamino)phosphoniumhexafluorophosphate (AOP)[59] (*Figure 1.4.1.4.2*) and (7-azabenzotriazol-1-yloxy)tris-(pyrrolidino) phosphoniumhexa-fluorophosphate (PyAOP),[59] have also been prepared and found to be more efficient than HOBt based phosphonium salt type coupling reagents.

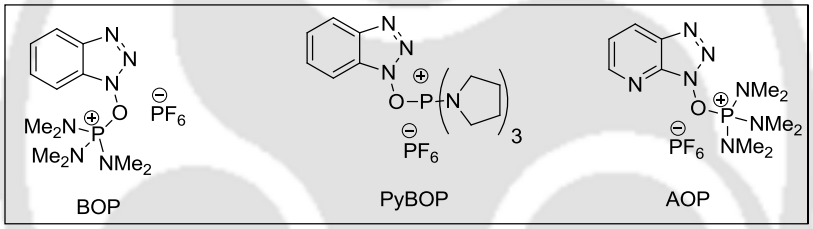


Figure 1.4.1.4.2. Phosphonium salt based coupling reagent

El-Faham and Albericio reported a phosphonium salt of Ethyl (hydroxyimino) cyanoacetate (Oxyma), *O*-[(cyano-(ethoxycarbonyl)methylidene)-amino]yloxytri-pyrrolidinophosphonium hexafluorophosphate (PyOxm, *Figure 1.4.1.4.3*),[60] as an efficient racemization suppressing coupling reagent for the assembly of hindered peptides. Oxyma performs better than classical benzotriazole. Similarly, the recently introduced uronium salt of Oxyma based regent such as 1-[(1-(cyano-2-ethoxy-2-oxoethylideneaminooxy)-dimethylamino-morpholinomethylene)] methanaminium hexafluorophosphate (COMU)[61] (*Figure 1.4.1.4.4*), renders a higher percentage of cyclic peptides than other known phosphonium salts in cyclization models.

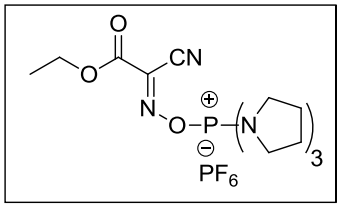


Figure 1.4.1.4.3. Schematic structure of PyOxm

Aminium salts or uronium salts based coupling reagents bear a positive carbon atom instead of the phosphonium residue. The amminium or uronium based reagents react with carboxylic acids to form HOAt/HOBt derived active esters, which then react with amines to form amide. Many coupling reagents based on the HOBt/HOAt system and uronium/aminium salts have been developed, such as *O*-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU) [62] (*Figure 1.4.1.4.4*), *etc*.

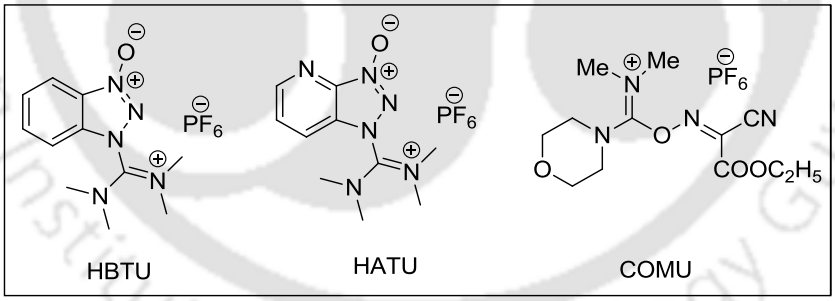


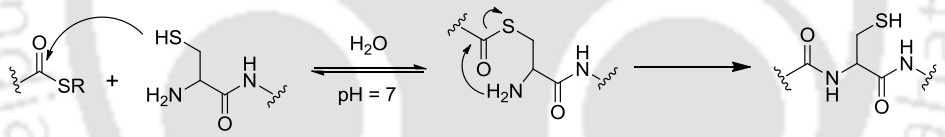
Figure 1.4.1.4.4. Uronium salt based coupling reagent

Although, most of these coupling reagents were efficient for coupling reaction, they suffers from some common drawback, including cabodiimide based reagents need additive for racemization suppression, whereas most of the phoshonium salt and uronium based reagents generated unwanted side product (Example, HMPA). Therefore, to

overcome those drawbacks, development of new coupling reagent is necessary, but challenging.

1.4.1.5. Synthesis of peptides via Native Chemical Ligation (NCL)

Native Chemical Ligation (NCL)[63] is a process where two fully unprotected peptide sequences can be joined in water at or around neutral pH, first reported by Kent and co-worker in 1994. For NCL reaction, the *C*-terminus must contain a thioester and the *N*-terminus a cysteine residue, in first step the sulfhydryl group of which undergoes a reversible transthioesterification reaction with the thioester moiety and second step the free amine is brought into close enough proximity for a spontaneous rearrangement to occur, yielding an amide bond (*Scheme 1.4.1.5.1*).



Scheme 1.4.1.5.1. NCL with thioester

One limitation of NCL is the requirement of a cysteine residue for the reaction to occur. Cysteine occurs with a low frequency relative to other amino acids in both proteins and cyclic peptides. Indeed many peptide sequences do not possess a cysteine at a site, the choice of which would allow division into appropriately sized portions for synthesis and subsequent NCL.

1.4.2. Solid phase peptide synthesis

In 1963, Prof. Robert Bruce Merrifield pioneered solid phase peptide synthesis (SPPS) for the chemical synthesis of peptides.[33] SPPS is a milestone in the area of peptide synthesis.

General steps of SPPS involve:

1. Loading of *C*-terminal amino acid to resin.

2. Deprotection of *N*-protected amino acid residue with the appropriate reagent.

3. Coupling of the next amino acid residue.

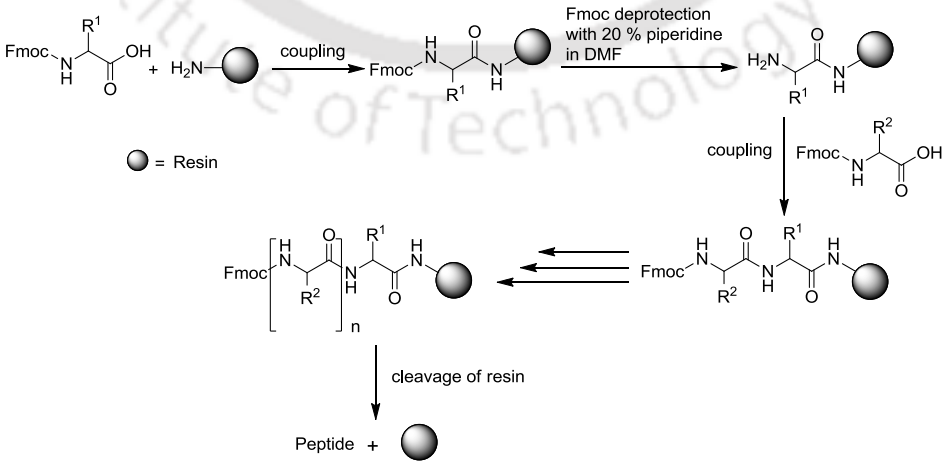
4. Chain elongation by cycling step **1** and **2**.

5. Cleavage from the resin to get the desire peptide.

Two important strategies of this method are Fmoc based SPPS and Boc based SPPS.

1.4.2.1. Fmoc based SPPS

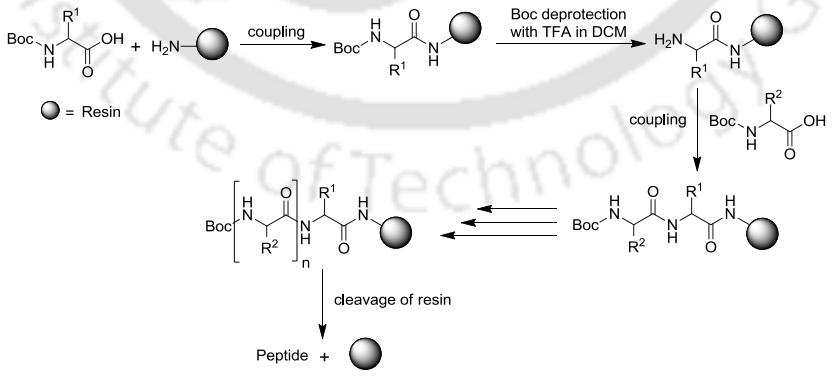
In Fmoc based SPPS,[64] first Fmoc protected amino acid is attached to resin via an acid labile linker followed by deprotection of Fmoc group, which is usually carried out by piperidine. The second Fmoc protected amino acid is coupled utilizing a pre-activated species or in situ activation by coupling reagents, such as HBTU, BOP, BOP-Cl, HATU, *etc*. After the synthesis of the desired peptide, the resin bound peptide is deprotected and detached from the resin (*Scheme 1.4.2.1.1*).



Scheme 1.4.2.1.1. Fmoc based SPPS

1.4.2.2. Boc based SPPS

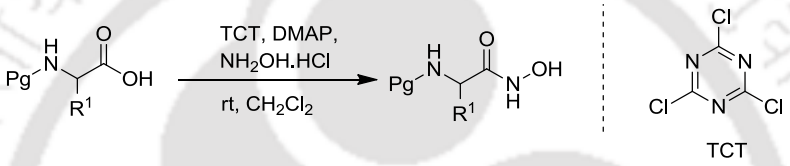
The general scheme 1.4.2.2.1 which outlines the strategy of Boc based SPPS.[65] Boc protected amino acid is first attached to the resin of HF cleavable linker. Deprotection of Boc of the resin connected amino acid is then performed by the treatment with TFA. Next, Boc protected amino acid then coupled utilizing a pre-activated species or through *in situ* activation. After the desired peptide has been synthesized, the resin bound peptide then cleaved from the solid support by HF treatment. HF is a highly dangerous gas, forming hydrofluoric acid upon contact with moisture which is highly corrosive and toxic. HF is handled under fume hood wearing with protective gloves, protective clothing, eye protection, face protection, *etc*. For many years, DCC has been the primary choice as coupling reagent for that strategy. The major problems encountered were the precipitation of dicyclohexyl urea during the activation and acylation processes and side reactions associated with its usage. Later, many new activating agents, such as PyBroP, PyBOP, and BOP were developed for performing Boc chemistry.



Scheme 1.4.2.2.1. Boc based SPPS

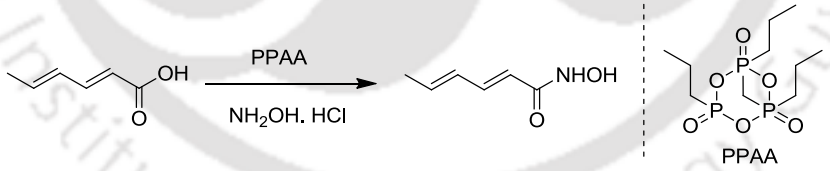
1.5. Existing methods for the synthesis of hydroxamates

Normally hydroxamic acids are synthesized by reaction between carboxylic acid and hydroxylamine hydrochloride in presence of various catalysts and reagents. Several methods are reported such as Giampaolo *et al.* reported a method for the synthesis unprotected hydroxamic acid from *N*-protected amino acid and hydroxylamine hydrochloride using cyanuric chloride (TCT) and *N*, *N*-dimethylaminopyridine (DMAP) (*Scheme 1.5.1*).[66]



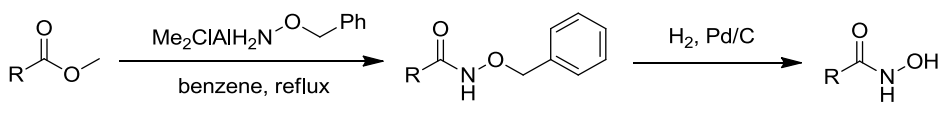
Scheme 1.5.1. Synthesis of hydroxamic acids using TCT

Appendino *et al.* illustrated a method for the synthesis of hydroxamic acids directly from α, β-unsaturated carboxylic acid and hydroxylamine hydrochloride using cyclic phosphonic anhydride (PPAA) (*Scheme 1.5.2*).[67]



Scheme 1.5.2. Preparation of hydroxamic acids using cyclic phosphonic anhydride

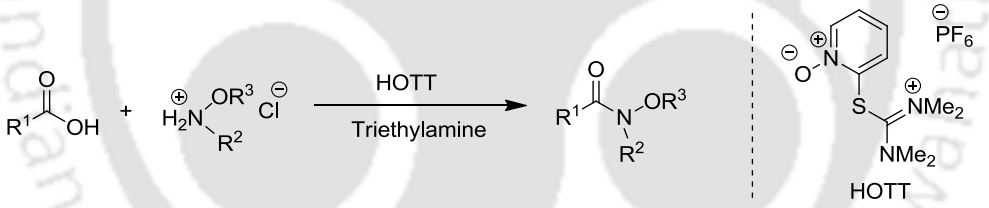
Pinung *et al.* synthesized amino acid based hydroxamic acid from amino acid ester and (*O*-Benzylhydroxylamine) methyl aluminum chloride in presence of benzene under reflux condition (*Scheme 1.5.3*).[68]



Scheme 1.5.3. Synthesis of hydraxamate from amino acid ester

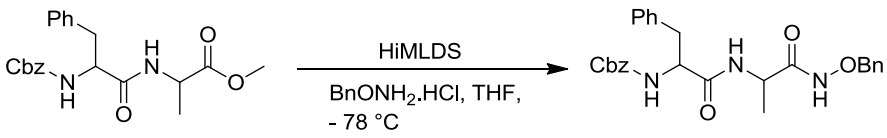
Handling of $AlMe_3$ is difficult because it is hazardous and very reactive species and benzene is used with it as solvent which is a carcinogenic solvent, therefore now it is banned. Again, TCT has been known to prepare from the dangerous precursor HCN and the byproduct comes from the reaction was extremely hygroscopic. Therefore, to overcome such difficulties, hydroxamic acids were prepared using peptide coupling reagents.

Najera *et al.* synthesized hydroxamates from carboxylic acid and *O*-benzylhydroxylamine hydrochlorides in the presence of thiouronium salt (*S*-(1-oxido-2-pyridinyl) 1,1,3,3-tetramethylthiouronium hexafluorophosphate (HOTT) (*Scheme 1.5.4*).[69] HOTT was prepared from the reaction of tetramethylurea or *N*, *N*-dimethylpropyleneurea (DMPU) with oxalyl chloride and a catalytic amount of DMF.



Scheme 1.5.4. Synthesis of hydraxamate using HOTT

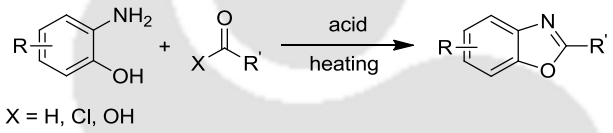
Zanda *et al.* reported one step method for the synthesis of hydroxamate derivatives directly from unactivated esters and the anion of *O*-benzyl-hydroxylamine was generated *in situ*. Using lithium hexamethyl disilylaizde (LIHMDSA) at –78 °C with no trace of racemization (*Scheme 1.5.5*).[70]



Scheme 1.5.5. Synthesis of hydraxamate from unactivated ester

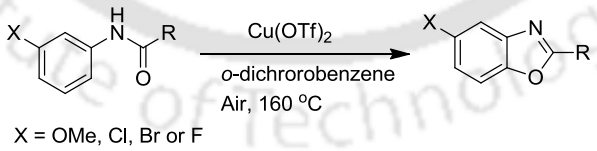
1.6. Existing methods for the synthesis of benzoxazoles and benzothiazoles

Traditional methods for the synthesis of benzoxazole and benzothizole derivatives take account the condensation of *o*-aminophenols with carboxylic acids or aldehydes, followed by oxidative cyclization using strong acids or with the use of stoichiometric amount of oxidant (*Scheme 1.6.1*).[71] These reaction involved harsh conditions, such as use of strong acids and elevated temperature (~210 °C).[72] Therefore, to perform such reactions some safety concerns must be undertaken.



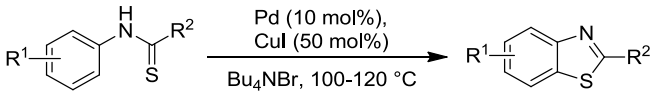
Scheme 1.6.1. Classical methods for synthesis of benzoxazole derivatives

Nagasawa *et al.* illustrated a method for the synthesis of benzoxazole derivatives form intramolecular coupling of anilides in presence of a copper (II)-catalyst, regioselective C-H functionalization/C-O bond formation using dichlorobenzene as solvent at 160 °C and air as a terminal oxidant (*Scheme 1.6.2*).[73]



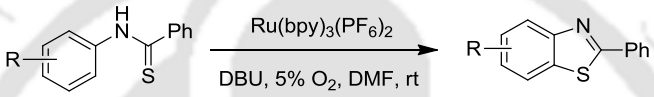
Scheme 1.6.2. Synthesis of benzoxazole derivatives using copper (II) catalyst

Inamoto *et al.* synthesized 2-substituted benzothiazoles from thiobenzanilides in presence of a palladium catalyst via C-H functionalization/C-S bond formation using Bu_4NBr at 100-120 °C (*Scheme 1.6.3*).[74]



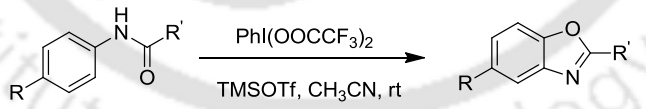
Scheme 1.6.3. Palladium Catalyzed C-H functionalization/*C-S* bond formation

Li *et al.* reported a method for the synthesis of benzothiazoles from thiobenzanilides in presence of visible-light photoredox via a radical C-H functionalization/C-S bond formation using dioxygen as the terminal oxidant (*Scheme 1.6.4*).[75]



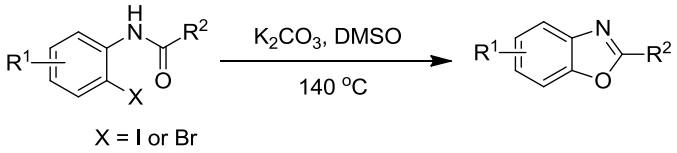
Scheme 1.6.4. An aerobic visible-light driven synthesis of benzothiazoles

Yu *et al.* illustrated a method for the synthesis of substituted benzoxazoles derivatives by intramolecular oxidative C-O bond formation of anilides using phenyliodine bis(triflouoroacetate) and Trimethylsilyl trifluoromethanesulfonate (TMSOTf) (*Scheme 1.6.5*).[76] These reaction conditions are limited to only electron rich *N*-phenyl benzamides.



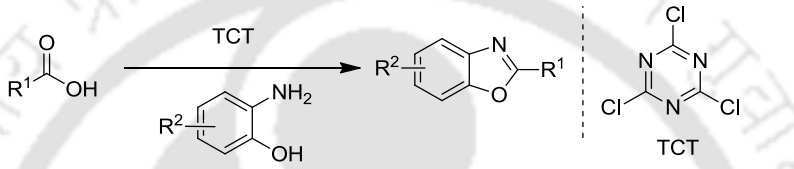
Scheme 1.6.5. Hypervalent iodine mediated synthesis of benzoxazoles

Chen *et al.* developed a method in which a direct base-mediated intramolecular carbon-oxygen bond formation without a transition-metal catalyst in the presence of K_2CO_3 in DMSO at 140 °C, the intramolecular cyclization of *o*-haloanilides affords benzoxazoles (*Scheme 1.6.6*).[77]



Scheme 1.6.6. Metal-free synthesis of benzoxazoles

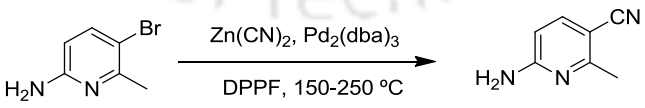
Nieddu *et al.* illustrated a metal free method for the synthesis of benzoxazole derivatives from carboxylic acid or *N*-protected amino acid and *o*-amino phenol by using TCT at room temperature (*Scheme 1.6.7*).[78]



Scheme 1.6.7. Metal-free synthesis of benzoxazoles using TCT

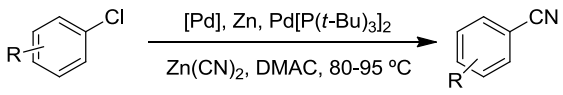
1.7. Existing methods for the synthesis of nitriles

Generally synthesis of nitrile was reported as the reaction between alky halide/aryl halide with a stoichiometric amount of inorganic cyanide or organic based cyanide. For example, Maligres *et al.* reported a method for the synthesis of aromatic nitrile from aryl bromide by using stoichiometric amount of CuCN and catalyst palladium in presence of DMF and l, l'-bis(diphenylphosphino)ferrocene (DPPF) ligand at 120-250 °C (*Scheme 1.7.1*).[79]



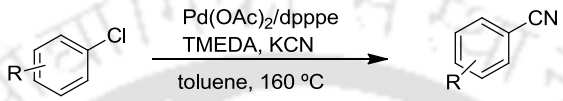
Scheme 1.7.1. Synthesis of nitrile using palladium

Littke *et al.* synthesized aryl cyanide from aryl chlorides using palladium-based catalyst systems, *N*,*N*-dimethylacetamide (DMAC) as a solvent and $Zn(CN)_2$ as a cyanide source at 80-95 °C (*Scheme 1.7.2*).[80]



Scheme 1.7.2. Synthesis of nitrile using palladium and zinc

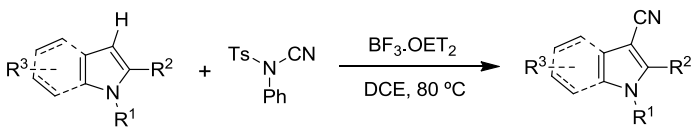
Beller *et al* have shown that palladium-catalyzed cyanation of activated aryl chlorides was performed using KCN as cyanide source (*Scheme 1.7.3*).[81]



Scheme 1.7.3. Synthesis of nitrile using palladium and KCN

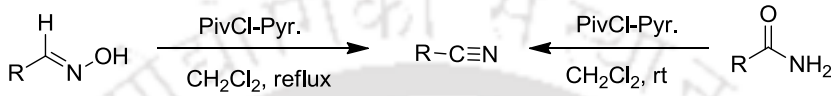
In spite of the wide application of the nitrile compounds, most of the methods of nitrile syntheses suffer from various drawbacks, of cyanide sources including the severe toxicity or the generation of stoichiometric amounts of metal wastes, which prevents their wide application in academic laboratory and the pharmaceutical industry. Moreover, the efficiency of these transformations is hampered by the high affinity of cyanide toward transition-metal-based catalytic systems, which often results in the rapid formation of stable cyanide complexes and deactivation of transition-metal catalysts.

Wang *et al.* reported, BF_3OEt_2-catalyzed direct cyanation of indoles and pyrroles using a less toxic, bench-stable, and easily handled electrophilic cyanating agent *N*-cyano-*N*-phenyl-para-toluenesulfonamide (NCTS) affords 3-cyanoindoles and 2-cyanopyrroles in good yields with excellent regio selectivity. The substrate scope was also broad with respect to indoles and pyrroles (*Scheme 1.7.4*).[82]



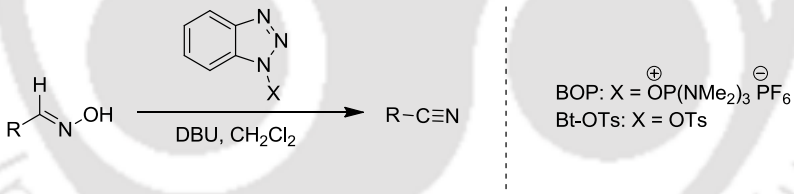
Scheme 1.7.4. Synthesis of nitrile using BF_3OEt_2-catalyst

Nagaiah *et al.* reported a method for the synthesis of nitrile from primary amide and aldoxime using pivaloyl chloride-pyridine system. The dehydration takes place at room temperature in the case of primary amides and dichloromethane at reflux temperature is required for rapid conversion in the case of aldoximes (*Scheme 1.7.5*).[83]



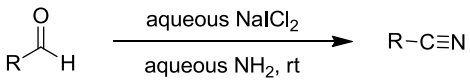
Scheme 1.7.5. Synthesis of nitrile using pivaloyl chloride-pyridine

Lakshman *et al.* illustrated a method for the synthesis of nitrile from aldoximes using 1*H*-benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP) or 1*H*-benzotriazol-1- yl-4-methylbenzenesulfonate (Bt-OTs) and DBU in CH_2Cl_2, THF, or DMF at room temperature (*Scheme 1.7.6*).[84]



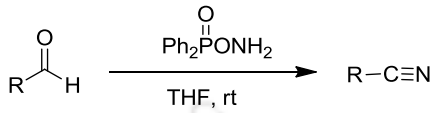
Scheme 1.7.6. Synthesis of nitrile using BOP and Bt-OTs

Telvekar *et al.* demonstrated nitrile synthesis from varieties of aldehydes using aqueous ammonia and aqueous sodium dichloroiodate reagent at room temperature. Advantages of this system were short reaction time, easy work-up and moderate to good yields (*Scheme 1.7.7*).[85]



Scheme 1.7.7. Synthesis of nitrile from aldehyde

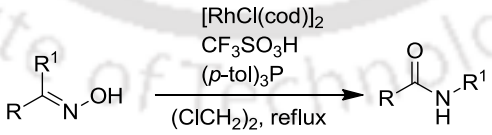
Nantz *et al.* illustrated a procedure for direct conversion of aldehydes to nitriles using *O*-(diphenylphosphinyl)hydroxylamine (DPPH) in toluene at reflux condition (*Scheme 1.7.8*).[86]



Scheme 1.7.8. Synthesis of nitrile using DPPH

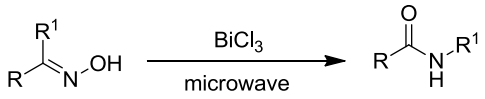
1.8. Existing methods for the synthesis of amides via Beckmann rearrangement

Synthesis of amides via Beckmann rearrangement (BKR) is one of the well-known methods in organic chemistry which include the synthesis of lactam from cyclic oximes. Several catalytic systems were reported including various inorganic catalysts as well as organocatalyst. For example, Yamaguchi *et al* reported amide synthesis via Beckmann rearrangement from ketoxime, catalyzed by $[RhCl(cod)]_2$, trifluoromethanesulfonic acid, and tris(*p*-tolyl)phosphine in dichloroethane under reflux condition, provided the corresponding amide in good yield (*Scheme 1.8.1*).[87]



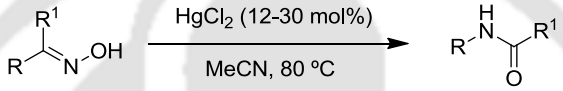
Scheme 1.8.1. Synthesis of amide using ruthenium catalyst

Sandhu *et al.* illustrated a method for the synthesis of amide from ketoxime via Beckmann rearrangement in presence of bismuth trichloride under microwave irradiation in the solid state (*Scheme 1.8.2*).[88]



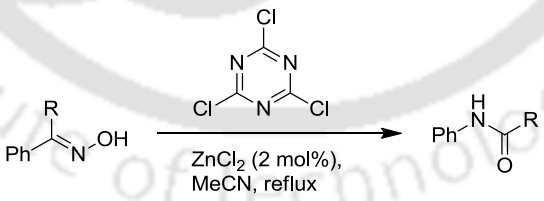
Scheme 1.8.2. Synthesis of amide using bismuth trichloride

Park *et al.* reported synthesis of amides/lactams using mercury (II) chloride in presence of acetonitrile with variety of acyclic and cyclic ketoxime at 80 °C with good to excellent yields (*Scheme 1.8.3*).[89]



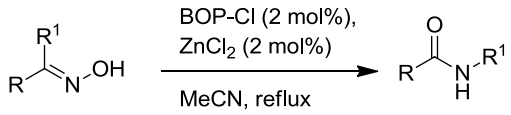
Scheme 1.8.3. Synthesis of amide using mercuric chloride

Due to handing difficulty and toxicity of these metals, recently, organo-catalyzed BKRs in liquid phase were reported because of their high efficiency and ease of handling. Ishihara *et al.* reported a first organocatalyst, cyanuric chloride (CNC) for the synthesis of amide via Beckmann rearrangement from oxime to amide (*Scheme 1.8.4*).[90]



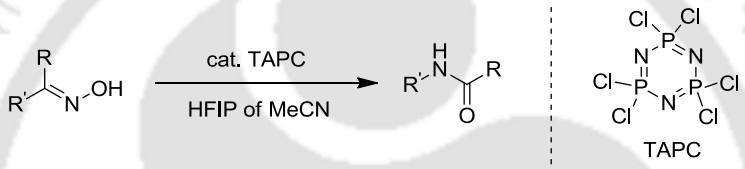
Scheme 1.8.4. Synthesis of amide using organocatalyst, cyanuric chloride

Shi *et al.* illustrated a method for the synthesis of amide from ketoxime via beckmann rearrangement by using commercially available BOP-Cl (5 mol%) or BOP-Cl (2 mol%) /$ZnCl_2$ (2 mol%) system (*Scheme 1.8.5*).[91]



Scheme 1.8.5. Synthesis of amide using organocatalyst, BOP-Cl

Ishii *et al.* reported 1,3,5-triazo-2,4,6-triphosphorine-2,2,4,4,6,6-chloride (TAPC), an organocatayst for the Beckmann rearrangement of cyclohexanone oxime and cyclododecanone oxime to ε-caprolactam and laurolactam (*Scheme 1.8.6*).[92]



Scheme 1.8.6. Synthesis of amide using organocatalyst, TAPC

1.9. Drawbacks of existing methods

Over the years, numerous coupling methods have been developed, for example, carboxylic halides, carboxylic azides, symmetrical or mixed anhydrides and coupling reagents based. Nonetheless, carboxylic chlorides and anhydrides are more reactive, and because of their reactivity, many side reactions are possible which are difficult to control. Acid labile *N*-protecting groups of amino acids get cleaved in presence of acid chloride. Therefore, application of the acid chloride method is restricted. In recent years two classes of coupling reagents became popular, the phosphonium- and the aminium- or uronium-type reagents. Most of them engage the benzotriazole or azabenzotriazole ring system as an important fragment of their structure, which is subsequently transformed into a good leaving group. After two decades of domination of benzotriazole-based chemistry, with the pioneering work of Albericio *et al.*, a new class of peptide coupling reagents, that is, ethyl 2-cyano-2-(hydroxyimino)acetate (Oxyma)-based reagents, have been introduced. Oxyma is superior to its counterparts as a racemization suppressant and environmentally friendly reagent. Nevertheless, existing popular coupling reagents still suffer from three major drawbacks. (a) Preparation protocols of these reagents involve harsh conditions and toxic reagents. For example HBTU is synthesized using phosgene (inflammable, causes skin damage) and HOBt (explosive) in carbon tetrachloride, a carcinogenic solvent. Similarly, 1-[(1-(cyano-2-ethoxy-2-oxoethylideneaminooxy) dimethylaminomorpholinomethylene)] methanaminium hexafluoro phosphate (COMU), an Oxyma-based coupling reagent, is also synthesized using phosgene. (b) Generation of chemical waste, for example, carcinogenic hexamethylphosphoramide (HMPA) and explosive hydroxybezotriazole (HOBt) are generated as byproducts when benzotriazol-1-yloxytris (dimethylamino)phosphonium-hexafluorophosphate (BOP) is used as coupling

reagent. (c) Furthermore, recycling those reagents may be challenging. Thus, they are not environmentally friendly.

1.10. Objectives of thesis

Based on the above observations, the aim of the thesis work is to design and synthesize a cost effective coupling reagent that would be easy to synthesize in laboratory as well as its byproducts would be recyclable, so that waste generation could be reduced. Also, the newly developed coupling reagent should be useful for the synthesis of many organic transformations as well as peptide synthesis. Based on these challenges, we have proposed the following objectives.

1 Introduction of an Oxyma based new coupling reagent, ethyl 2-cyano-2-(2-nitrobenzenesulfonyloxyimino)acetate (*ortho*-NosylOXY or *o*-NosylOXY) and its application for the racemization free synthesis of amides & peptides.

2 Synthesis of esters and hydroxamates using *o*-NosylOXY.

3 Synthesis of benzoxazoles and benzothiazoles directly from carboxylic acid in solution and on solid supported resin using *o*-NosylOXY and *p*-toluene sulfonic acid.

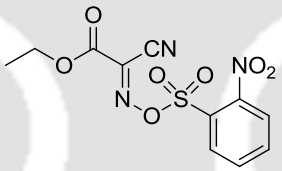
4 Synthesis of nitriles from aldoxime using *o*-NosylOXY.

5 Synthesis of amides via Beckmann rearrangement using *o*-NosylOXY.

Chapter 2: Ethyl 2-Cyano-2-(2-nitrobenzenesulfonyloxyimino)acetate (*o*-NosylOXY): A New Coupling Reagent for Racemization-Free Synthesis of Amide and Peptide

Amide bond formation is one of the most important reactions in organic chemistry, which is often overlooked as a contemporary challenge in spite of the widespread occurrence of amides in modern pharmaceuticals and biologically active compounds (Chapter1, section 1.3.1). From the last two decades, a great effort has been devoted towards the development of efficient methods for the synthesis of amides and peptides from carboxylic acids and *N*-protected amino acids using various coupling reagents (Chapter 1, section 1.4). Till date, numerous coupling reagents have been developed and commercialized including carbodiimides, phosphonium, and uronium/ aminium salts.[32, 93-95] Most of them contained the benzotriazole or azabenzotriazole ring system as an important fragment of their structure, which is subsequently transformed into a good leaving group.[96] After two decades of domination of benzotriazole-based reagents, with the pioneering work of Albericio *et al.*, a new class of peptide coupling reagents, that is, ethyl 2-cyano-2-(hydroxyimino)acetate (Oxyma) based reagents, have been introduced.[97-98] Oxyma is superior to its counterparts as racemisation suppressant and environmentally benign reagent.[99] Moreover, a major drawback of existing coupling reagents

(carbodiimide, HOBt, and Oxyma based coupling reagents) is the generation of substantial amount of undesired byproduct. Furthermore, most of these coupling reagents are often very difficult to synthesize, involves multi-step synthesis and requires harsh conditions. Therefore, the invention of an environmentally benign and cost effective coupling reagent with highest level of efficacy and lowest level of epimerization still remains a challenge for the scientists and researchers. To address the challenges, herein, we have developed a new coupling reagent, Ethyl 2-Cyano-2-(2-nitrobenzenesulfonyl-oxyimino)acetate (*o*-NosylOXY), which is easy to synthesize, stable at room temperature for long time and is recyclable. In this chapter, we have shown the application of the reagent (*o*-NosylOXY) for the racemization free synthesis of amide and peptide.

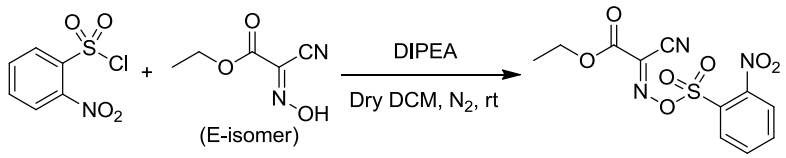


I

Figure 2.1. Ethyl 2-cyano-2-(2-nitrobenzenesulfonyloxyimino)acetate (*ortho*-NosylOXY, **I**)

2.1. Reaction optimization and substrate scope for amides and peptides synthesis using *ortho*-NosylOXY

We synthesized the newly designed coupling reagent, *o*-NosylOXY, by reacting *o*-nitrobenzenesulfonyl chloride (*o*-Nosyl-Cl) and (E)-ethyl-2-cyano-2-(hydroxyimino)acetate (Oxyma) in presence of DIPEA at room temperature under nitrogen for 2 h (*Scheme 2.1.1*). The *o*-NosylOXY is stable at room temperature for long time. The time dependent HPLC and ^{1}H NMR studies of the reagent indicated no change till 20 days.



Scheme 2.1.1. Preparation of reagent **I**

To check the coupling efficiency of the newly developed coupling reagent, *o*-NosylOXY, we first optimized the reaction condition (*Table 2.1.1*). For optimization, we added DIPEA in the solution of phenylacetic acid and reagent **I** in defferent solvent, including EtOAc, THF, CH_3Cl, DCM, DMF, DMSO or acetonitrile. After 5 min preactivation of the reaction mixture benzylamine was added and the rection mixture was further kept in stirring condition at room temperature for 2 h. We observed the DCM was the best suitable solvent for the reagent preparation with an excellent yield (91%) of the desired product.

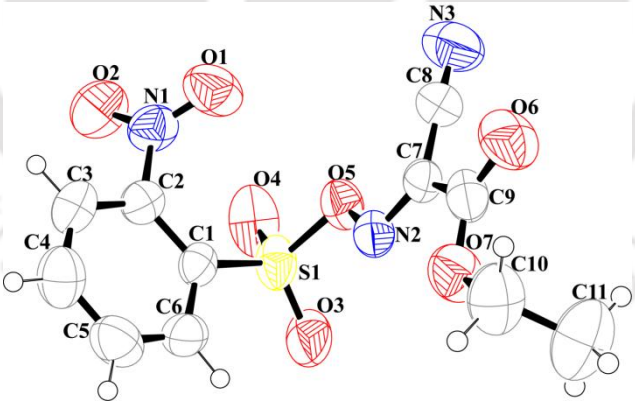
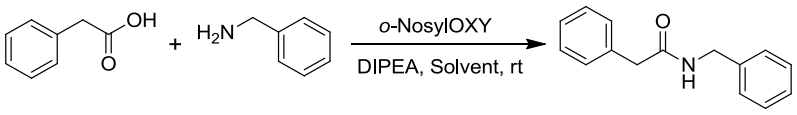


Figure 2.1.1. X-ray crystallographic structure of *o*-NosylOXY (ORTEP diagram with ellipsoid of 50% probability, CCDC No. 903881)

Table 2.1.1. Solvent screening[a]

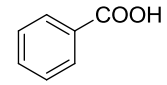
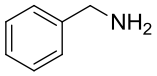
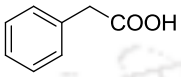
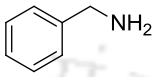
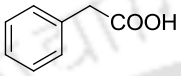
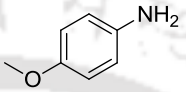
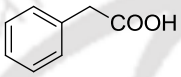
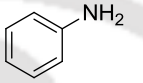
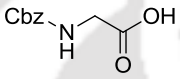
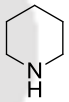
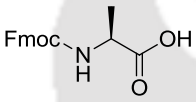
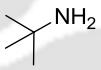
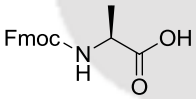
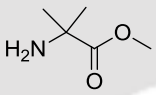
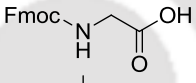
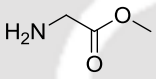
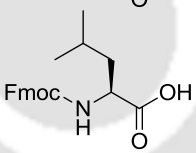
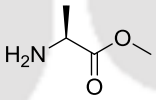
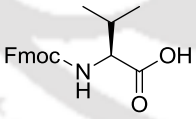
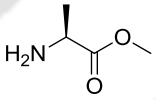
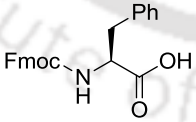
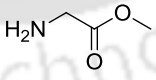
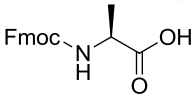
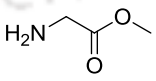
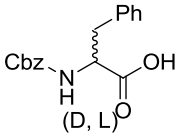
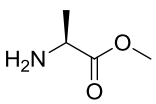
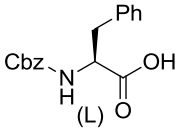
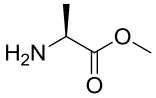


Entry	Solvent	Yield (%)[b]	Time (h)
1	Acetonitrile	67	8
2	DMSO	56	11
3	THF	48	13
4	DMF	85	3
5	DCM	91	2.2
6	Ethyl acetate	70	5
7	Chloroform	78	3

[a]*Performed with phenylacetic acid (1 equiv), Reagent* ***I*** *(1 equiv), DIPEA (2.2 equiv), benzylamine (1 equiv), room temperature.* [b]*Yields refer to the isolated yield after column chromatography.*

Using the optimized conditions, we explored the scope of the amidation and peptide synthesis, by studying the reactivity of various aromatic carboxylic acids, aliphatic carboxylic acids and *N*-protected amino acids with variety of amines and methyl ester of amino acids. We observed, the reaction worked well with the less nucleophilic amine, aniline (*entry 4, Table 2.1.2*) and hindered secondary amine (*entry 5*) as well as hindered primary amine (*entry 6*), with excellent yields. The current protocol was also compatible with common *N*-protecting groups, including Cbz (*entries 5, and 13-18*) and Fmoc (*entries 6-12*). Furthermore, the reaction worked smoothly for sterically hindered *N*-protected amino acids, e.g. Val (*entry 10*) and Aib (*entries 16 and 17*), as carboxylic acid component as well as methyl ester of Aib (*entry 7*), Val (*entry 18*) and tertiary butylamine (*entry 6*), as amine component, which are known to be difficult for coupling. Yield of desired products was also found good to excellent (up to 93%, *Table 2.1.2*).

Table 2.1.2. Scope of the amide and peptide synthesis using reagent *o*-NosylOXY[a]

Entry	Carboxylic acid	Amine	Yield (%)[b]
1			88
2			91
3			82
4			86
5			89
6			81
7			80
8			91
9			89
10			87
11			93
12			87
13			90
14			91

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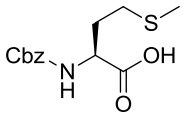
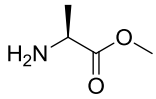
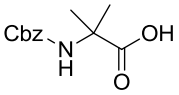
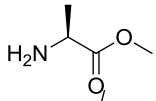
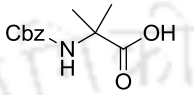
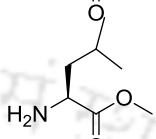
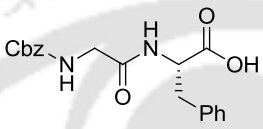
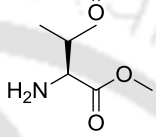
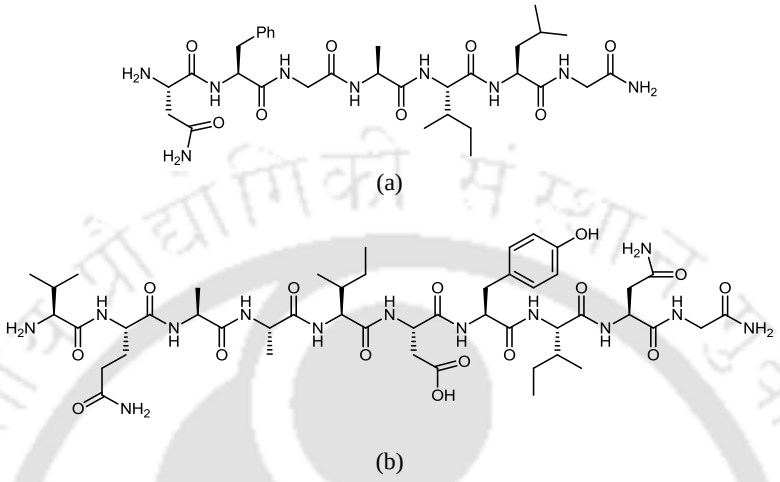
15			89
16			81
17			78
18			91

[a]*Performed with carboxylic acid (1 equiv), reagent* ***I*** *(1 equiv), DIPEA (2.2 equiv), amine (1 equiv) or methyl ester of amino acid (1.1 equiv), room temperature, 2-3 h.* [b]*Yields were referred to the isolated yields after column chromatography.*

We also demonstrated the reaction between Fmoc-Phe-OH and NH_2-Ala-OMe in the presence of *o*-nitrobenzenesulfonyl chloride as a coupling reagent to verify utility of the Oxyma part in reagent **I**. In that case, we obtained dipeptide, Fmoc-Phe-Ala-OMe, with 65% yield and sulfonamide, *o*-nitrobenzenesulfonamide of methyl ester of alanine, with 10% yield. We also observed ~10% racemization, detected by HPLC profile of the dipeptide (*Figure S20-S22*).

Further we extended the scope of the reagent **I** for the synthesis of two long chain polypeptides using Fmoc/^{t}Bu orthogonal protection technique based SPPS (Solid Phase Peptide Synthesis) method. First, fragment of hIAPP (22-27)[100] peptide (hIAPP, Human Islet Amyloid Poly Peptide: H-Asn-Phe-Gly-Ala-Ile-Leu-Gly-NH_2, *Figure 2.1.2a*) and second ACP (65-74)[101] peptide fragment (ACP, Acyl Carrier Protein: H-Val-Gln-Ala-Ala-Ile-Asp-Tyr-Ile-Asn-Gly-NH_2, *Figure 2.1.2b*). Both are known as difficult sequences

for synthesis because they contain many hydrophobic amino acids which undergo conformational change resulting in aggregation during the synthesis process.



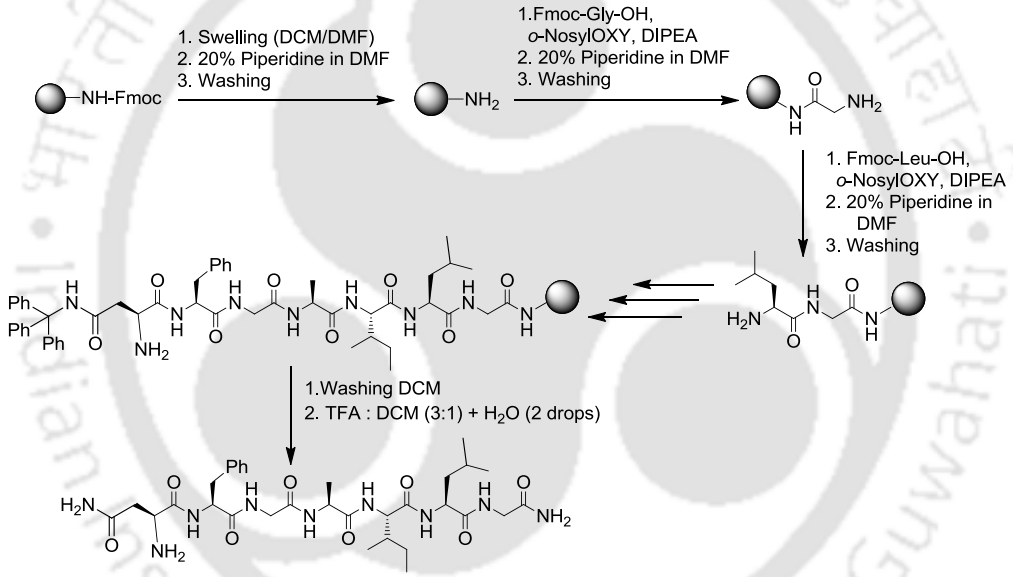
(a)

(b)

Figure 2.1.2. Sequences of peptides synthesised: (a) NFGAILG-NH_2 and (b) VQAAIDYING-NH_2 using SPPS

Both of the peptide hIAPP (22-27, stepwise coupling shown in *scheme 2.1.2*) and ACP (65-74) fragments were synthesized by stepwise coupling of constituent amino acids on Rink Amide MBHA resin using **I** as a coupling reagent following Fmoc/^{t}Bu orthogonal protection technique based SPPS method. 3.2 fold excess of the Fmoc amino acids and 3 fold excess of the coupling reagents were used for each coupling step. Important point to note was that the excess reagent (**I**) was avoided to prevent truncation or the side reaction of sulfonamide formation. Each coupling was completed smoothly in 2 h and the coupling was monitored by Kaiser's test. Complete coupling of each steps were also monitored by micro cleavage test using HPLC and ESI-MS. The HPLC retention times and ESI-MS data for each fragment during the synthesis of hIAPP (22-27) were depicted in table 2.1.4. The final peptide was cleaved from the resin using TFA/DCM/H_2O (9/0.5/0.5) mixture followed by ether precipitation and purified by semi-preparative HPLC. The yield of the

purified products was observed for hIAPP (22-27) 40% and ACP (65-74) fragment 50% with respect to the resin loading. The HPLC profiles and ESI-MS spectra of hIAPP (22-27) and ACP (65-74) were depicted in Figures S25-S26 and S29-S30 respectively. Quality of the crude peptide also was excellent. As an example, that for the peptide ACP (65-74) was compared with the reported data (*Table 2.1.3*).[101] Quality of the crude IAPP (22-27) peptide fragment synthesized using **I** as coupling reagent was also very good (*HPLC profile, Figure S23*).



Scheme 2.1.2. Synthesis of peptide sequence NFGAILG-NH_2 on SPPS using reagent **I**

Table 2.1.3. Comparative study of the purity of crude ACP (65-74) by TBTU, HATU, TBCR and *o*-NosylOXY

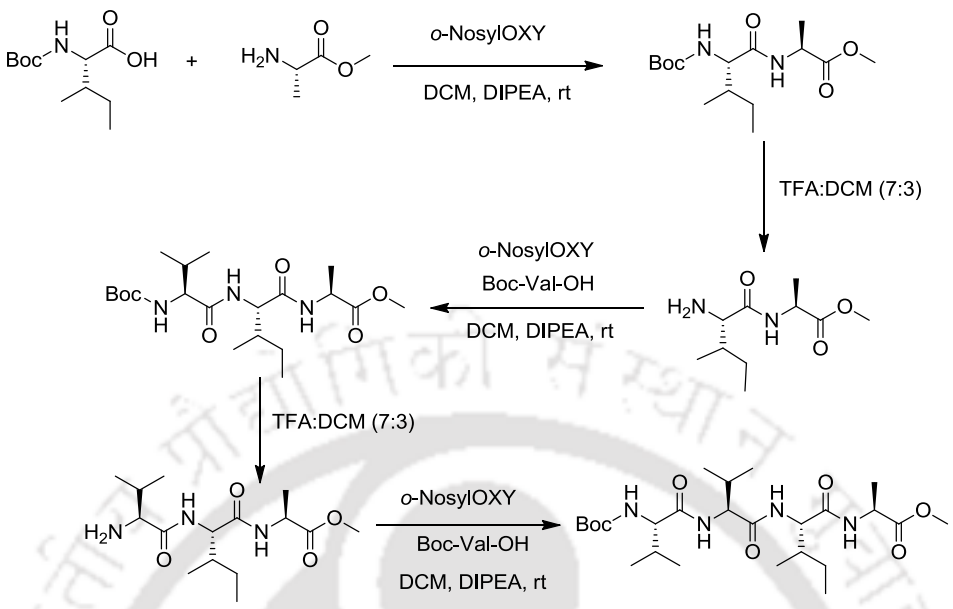
Coupling reagent	Purity of crude ACP (65-74) [%]
TBTU	69
HATU	87
TBCR	84
o-NosylOXY	90[a]

[a]*purity of the crude peptide could be detected by HPLC (Figure S27).*

Table 2.1.4. HPLC retention times and observed mass (ESI-MS) of the peptides after each coupling step for SPPS of IAPP (22-27)

Entry	Peptide	Retention time of HPLC (in min.)	Expected mass (m/z)	Observed mass (m/z)
1	Fmoc-LG-NH_2	12.10	$[M+Na]^+$ 432.18	432.19
2	Fmoc-ILG-NH_2	12.00	$[M+H]^+$ 523.12	523.15
3	Fmoc-AILG-NH_2	11.00	$[M+H]^+$ 594.32	594.34
4	Fmoc-GAILG-NH_2	12.05	$[M+H]^+$ 651.35	651.37
5	Fmoc-FGAILG-NH_2	14.02	$[M+H]^+$ 798.41	798.44
6	Fmoc-NFGAILG-NH_2	13.30	$[M+H]^+$ 912.46	912.49
7	NFGAILG-NH_2	11.50	$[M+H]^+$ 690.39	690.39

We also synthesized Boc-Val-Val-IIe-Ala-OMe, the *C*-terminal fragment of the amyloid β peptide[102] following solution phase methodology using Boc-chemistry based stepwise coupling (*Scheme 2.1.3*). The peptide was also known as difficult sequence for synthesis due to high hydrophobicity and huge steric hindrance. We observed reasonably good yield (78%, after five steps with respect to starting Boc-Ile-OH) and clean HPLC chromatogram of the crude peptide (*Figure S18*), which was as good as the purified peptide.



Scheme 2.1.3. Synthesis of Boc-Val-Val-IIe-Ala-OMe using Boc-chemistry in solution phase

2.2. Racemization study

We checked the racemization suppression efficiency of the reagent **I** during the synthesis of amide and peptide. For that, we synthesized Z-DL-Phe-L-Ala-OMe and Z-L-Phe-L-Ala-OMe using **I** and compared their HPLC profiles (*Figure 2.2.1*). Appearance of the two peaks in the HPLC profile of Z-DL-Phe-L-Ala-OMe corresponded to the two diastereomeric products, whereas, presence of the single peak in that of Z-L-Phe-L-Ala-OMe demonstrated virtually no racemization occurred during the synthesis. The comparison of the ^{1}H and ^{13}C NMR spectra of these dipeptides also supports the hypothesis (*Figure S5-S8*). We found two doublets in ^{1}H NMR at δ = 1.32 and 1.21 ppm and similarly four peaks at δ = 173.0, 172.9, 170.9 and 170.7 ppm in ^{13}C NMR of Z-DL-Phe-L-Ala-OMe, which indicated the presence of two diastereomers. Whereas, we found one doublet at δ = 1.32 ppm in the ^{1}H NMR and two peaks at δ = 173.0 and 170.7 ppm in ^{13}C NMR for Z-L-Phe-L-Ala-OMe indicating the presence of one diastereomer. From the

HPLC profiles, ^{1}H NMR and ^{13}C NMR, it can be concluded that there was no racemization during the synthesis of amide and peptide by using reagent **I** as a coupling reagent.

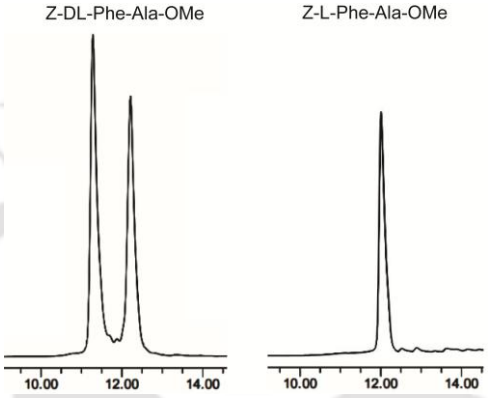


Figure 2.2.1. Comparison of the HPLC profiles of Z-DL-Phe-L-Ala-OMe (left panel) and Z-L-Phe-L-Ala-OMe (right panel) (C18 reverse phase analytical column, 5 µm, 25 cm× 4.6 mm, linear gradient of 0-80 %, 0-7 min. then 80-100 % upto 20 min., CH_3CN in H_2O with 0.1% formic acid**)**

Though, the supression of racemization is known to occur due to the presence of the *N*-terminal urethane protecting group.[103] To clarify any doubt, we compared our results with the reported data while the synthesis of a tripeptide, Z-Gly-Phe-Val-OMe (*entry 18, Table 2.1.2*), via coupling of Z-Gly-Phe-OH and H-Val-OMe using **I** and other well-known coupling reagents, such as, HBTU (*N*-[(1*H*-benzotriazol-1-yl)(dimethylamino) methylene] *N*-methylmethanaminium hexafluorophosphate*N*-oxide), HATU (*N*-[(dimethylamino)-1*H*-1,2,3-triazolo[4,5-b]pyridin-1-yl-methylene)-*N*-methylmethan-aminium hexafluorophosphate-*N*-oxide), HDMB (1-((dimethylamino)- (morpholino) methylene)-1*H*-benzotriazolium hexafluorophosphate-3-oxide) and HDMA (1-((dimethylamino)-(morpholino)methylene)-1*H* [1,2,3]triazolo[4,5-b]pyridinium-hexafluorophosphate3-oxide) in solution.[104] No racemization was detected, when reagent

I was used, examined by HPLC and NMR technique, however, some epimerization was noted for other reagents (*Table 2.2.1*).

Table 2.2.1. Comparison of yield and racemization tendency for the formation of Z-Gly-Phe-Val-OMe using *o*-NosylOXY (**I**) with the reported[104] results using various coupling reagents.

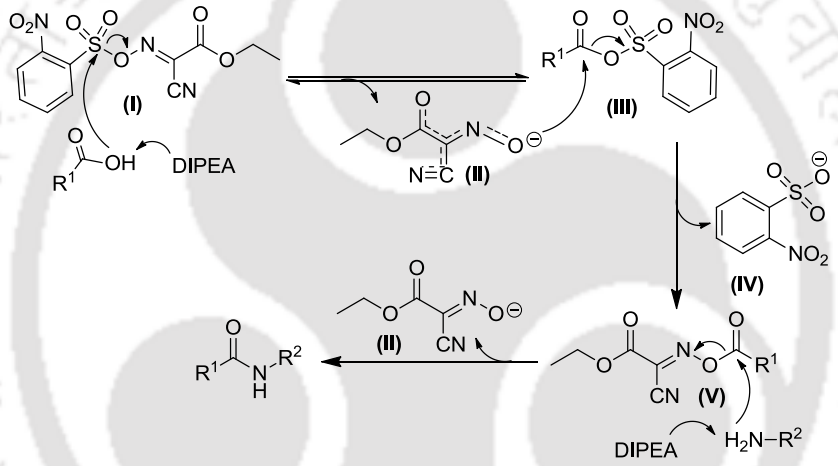
Entry	Coupling Reagent	Yield (%)	Racemization (%)
1	HBTU	89	5.90
2	HATU	90	1.56
3	HDMB	90	2.90
4	HDMA	90	0.65
5	*o*-NosylOXY	91	n. d.[a]

[a]*No racemization could be detected by the ^{1}H and ^{13}C NMR spectra and the HPLC profile (Supporting Information, Figures S9- S10 and S16) within the limit of our experimental condition.*

2.3. Plausible mechanism

A plausible mechanism is depicted in scheme 2.3.1. Initially, the nucleophile attacked to the more electrophilic sulfonyl center of **I** which was generated by the deprotonation of the carboxylic acid in presence of DIPEA resulted the mixed anhydride **III** after expulsion of the resonance stabilized Oxyma anion **II**. Further, the nucleophilic attack of **II** on the carbonyl carbon of **III** and expulsion of the sulfonic acid **IV** resulted in the formation of the intermediate **V**, the activated Oxyma ester of the carboxylic acid. **V** underwent nucleophilic substitution to produce the corresponding amide. The intermediate **V** was isolated and and characterized by ^{1}H NMR, ^{13}C NMR (*Figure S3-S4*) and single crystal XRD (*Figure 2.3.1*). However, the added nucleophile (amine) may also react with the intermediate **III**. But, in that case, sulfonamide also may get generated as

byproduct and racemization of the product is expected, as it was observed when the reaction was performed without pre-activation or using *o*-nitrobenzenesulfonyl chloride. A 3-5 min preactivation precludes that possibility by increasing the population of the intermediate **V** in the reaction mixture. DCM, is a polar aprotic solvent, enough to dissolve the substrate and nucleophile, but do not participate in hydrogen bonding with the nucleophile. If we use polar protic solvent such as, MeOH, BuOH, *etc*. which form hydrogen bonding with nucleophile and stable compound *o*-nosyl ester with **I**.



Scheme 2.3.1 Plausible pathways for the condensation

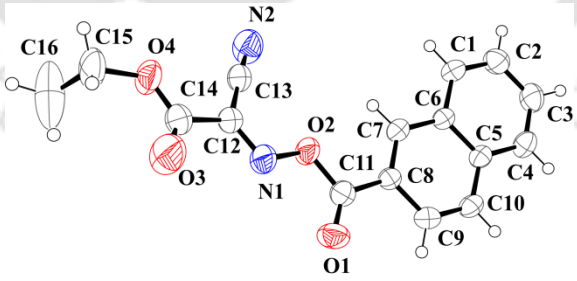
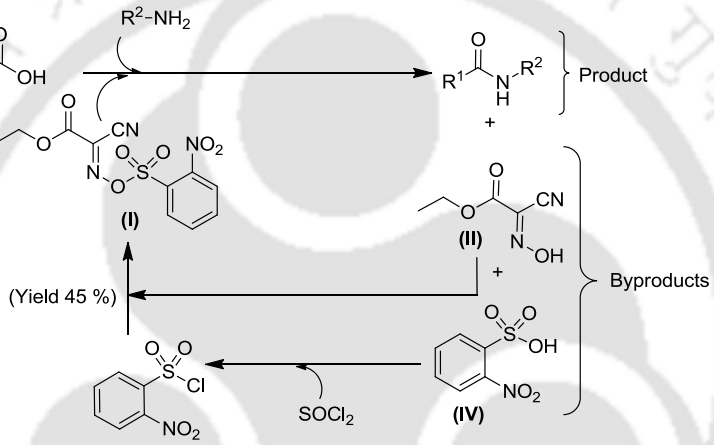


Figure 2.3.1. X-ray crystallographic diagram of the intermediate **V** (ORTEP diagram with ellipsoid of 50% probability, CCDC No. 936483).

2.4. Recyclability of *o*-NosylOXY

The by-products Oxyma (II) and 2-nitrobenzene sulfonic acid (IV) were recovered easily. After completion of the reaction, the reaction mixture was diluted with ethyl acetate and

washed with 5% citric acid solution (3×5 mL). Concentrated organic layer was directly purified by a silica gel column chromatography. The product and byproducts were eluted with specific eluents. The recovered sulfonic acid was chlorinated by heating at 60 °C for 1.5 h in toluene with a small amount of DMF using thionyl chloride. Pure sulfonyl chloride, obtained in this way, was transformed to reagent **I** by stirring with Oxyma under basic medium (DIPEA).



Scheme 2.4. Recyclability of coupling reagent **I**

2.5. Conclusion

We have developed a new and efficient coupling reagent, *o*-NosylOXY (**I**), for the synthesis of amide and peptide. The present method demonstrate apparently complete retention of stereochemistry and it work under ambient and milder conditions. The coupling reagent **I** has been successfully used for both solid phase and solution phase peptide syntheses. Preparation of the reagent **I** is easy and it is stable at room temperature for at least 20 days (checked using HPLC). A plausible mechanism has been suggested and an intermediate has been isolated and fully characterized. Most importantly, the reagent can be recyclable, therefore, cost effective and environment friendly.

2.6. Experimental section

2.6.1. General consideration

All reagents were purchased from commercial sources and were used without any further purification unless mentioned otherwise. The *o*-nitrobenzenesulfonyl chloride and DIPEA purchased from Sigma-Aldrich and DCM purchased from Merck. DCM is distilled and dried using standard procedure. Melting points were uncorrected. Thin layer chromatograms were run on glass plates coated with silica gel G for TLC, using solvent systems EtOAc/Hexane. Compounds were purified by column chromatography using Silica Gel (60-120 mesh) with EtOAc/Hexane (of specific proportion as required) as an eluent. ^{1}H NMR (400 MHz and 600 MHz) and ^{13}C NMR (100 MHz and 150 MHz) were recorded using $CDCl_3$ as solvent. Chemical shifts (δ) were reported in parts per million (ppm), internal reference (0.05% to 1%) tetramethylsilane. Coupling constants (*J*) are reported in Hz singlet (s), doublet (d), triplet (t), doublet of doublet (dd), multiplet (m), or broad (br). High resolution mass spectrometry (HRMS) was recorded on a Q-TOF ESI-MS instrument and a Q-TOF LC/MS system and GCMS were recorded on a gas chromatograph. HPLC analysis was carried out with either a C8 (5 µm, 3.5×150 mm) or a C18 (5 µm, 4.6×250 mm) reverse phase column and a chiral column (5 µm, 2.1×150 mm) attached with an UV detector. HPLC grade solvents were used for HPLC analysis. IR spectra were recorded on an IR spectrometer; X-ray data were collected on a diffractometer equipped with a CCD area detector using Mo. Optical rotation was recorded on Rudolph research analytical autopol II automatic polarimeter using one ml glass cell and chloroform as solvent. Data for previously reported compounds (cited) matched well with our observed data.

2.6.2. Procedure for the synthesis of the coupling reagent ethyl 2-cyano-2-(2-nitrobenzenesulfonyloxyimino)acetate (*o*-NosylOXY, I)

DIPEA (1 equiv) was added to a solution of Oxyma (1 equiv) in 2 mL of DCM under nitrogen. The reaction mixture was cooled up to 0 °C and *o*-nitrobenzenesulfonyl chloride (1 equiv) was added drop wise during 30 min. The reaction mixture was then stirred for another 2 h at room temperature. After completion of the reaction, the reaction mixture was diluted with 10 mL of DCM and washed with 5% of HCl (3×5 mL). Finally organic layer was dried by anhydrous $CaCl_2$ and recrystallized with hexane.

2.6.3. General procedure for the synthesis of amide

o-NosylOXY (1 equiv) was added to a solution of carboxylic acid (1 equiv) and DIPEA (1 equiv) in 2 mL of DCM. The reaction mixture was stirred for 3-5 min for pre-activation, followed by the addition of amine (1 equiv). The reaction mixture was stirred at room temperature for 2-3 h. After completion, the reaction mixture was diluted with 50 mL of ethyl acetate; the organic phase was washed with 5% citric acid (3×20 mL), 5% $NaHCO_3$ (3×20 mL) and dried by anhydrous Na_2SO_4. Finally, Na_2SO_4 was filtered off and the solvent was evaporated to obtain the product which was purified by column chromatography.

2.6.4. General procedure for the synthesis of dipeptides

To a solution of *N*-protected amino acid (1 equiv) and *o*-NosylOXY (1 equiv) in 2 mL of DCM, DIPEA (1.1 equiv) was added. The reaction mixture was stirred for 5 min for preactivation followed by the addition of methyl ester of the second amino acid (1.1 equiv) and DIPEA (1.1 equiv) in 1 mL of DCM. The reaction mixture was stirred at room

temperature for more 2-3 h. After completion, the reaction mixture was diluted with 50 mL of ethyl acetate, the organic phase was washed with 5% citric acid (3×20 mL), 5% $NaHCO_3$ (3×20 mL), brine and dried over anhydrous Na_2SO_4. Finally, Na_2SO_4 was filtered and the solvent was evaporated. The product was purified by silica gel column chromatography.

2.6.5. Synthesis of Boc-VVIA-OMe in solution phase

Boc-isoleucine (1 equiv) and *o*-NosylOXY (1 equiv) was taken in a 25 mL RB, after that DIPEA (1.5 equiv) was added and kept 5 min for pre-activation. In another oven dried 50 mL RB, methyl ester of alanine (1.5 equiv) was taken in DCM and DIPEA was added to it till basic pH was reached. Finally, that solution was added in first RB and stirring was continued until completion of the reaction. Then, the reaction mixture was diluted by 50 mL of EtOAc, washed by 5% $NaHCO_3$ solution (2×5 mL) and washed by 5% citric acid solution (2×5 mL). Finally, combined organic layer was dried using anhydrous Na_2SO_4. Solid product (Boc-IA-OMe) was obtained after evaporation of EtOAc by rotary vacuum evaporator.

In an oven dried 50 mL RB, Boc-IA-OMe was taken and 70% TFA solution in DCM was added to it. Stirring continued up to 2.5 h. After that, TFA was evaporated by rotary evaporator and washed 3 times with diethyl ether and finally white solid (IA-OMe) was obtained.

After Boc deprotection, resulted IA-OMe was coupled with Boc-V-OH following the above mentioned procedure to obtain Boc-VIA-OMe. Another cycle of Boc-deprotection and coupling with Boc-V-OH, resulted white solid Boc-VVIA-OMe, which was

characterized by reverse phase HPLC, retention time was 12.8 min on linear gradient of 20 to 100% CH_3CN/0.09% TFA in H_2O/0.09% TFA over 18 min, symmetry C8 analytical column and LRMS (ESI): m/z $[M+H]^+$ calculated for $C_{25}H_{47}N_4O_7$ is 537.3264 found 537.3421. Yield was 78% with respect to starting material Boc-isoleucine.

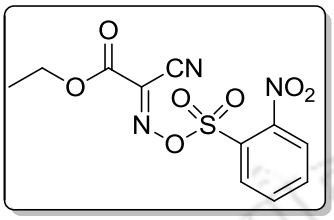
2.6.6. Solid phase synthesis of NFGAILG-NH_2 and VQAAIDYING-NH_2

Specific amino acids were manually assembled on Fmoc-Rink Amide MBHA resin (loading 1.1 mmol/g) following Fmoc-^{t}But orthogonal protection strategy. Fmoc-amino acids (3.2 equiv), *o*-NosylOXY (3 equiv) and DIPEA (5 equiv) was kept for pre-activation for 5 min. Amino acid coupling was performed for 2 h. Fmoc deprotection was carried out with 25% piperidine/DMF (3×7 min). The peptide was cleaved from the resin using TFA/DCM/H_2O (9/0.5/0.5) mixture for 2 h 30 min. Purification of the peptide was performed using semi-preparative HPLC using a linear gradient of 20 min (5 to 100% CH_3CN in water with 0.09% TFA) and characterized using ESI-MS.

For NFGAILG-NH_2, we took 300 mg of Fmoc-Rink Amide resin (loading 1.1 mmol/g), after final coupling, peptide was cleaved from resin and purified by semi-preparative HPLC. The purified yield of peptide was 90 mg, 40%, HPLC profile and ESI-MS spectrum (*Figure S25-S26*). And for VQAAIDYING-NH_2, we took 300 mg of Fmoc-Rink Amide resin (loading 1.1 mmol/g), after final coupling, this peptide was also cleaved from resin and purified by semi-preparative HPLC. Yield of the purified peptide was 175 mg, 50%. HPLC profile and ESI-MS spectrum are provided in *Figure S29-S30*.

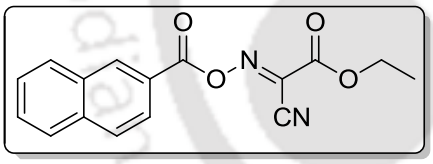
2.7. Characterization data

Ethyl 2-cyano-2-(2-nitrobenzenesulfonyloxyimino)acetate (*o*-NosylOXY, I)



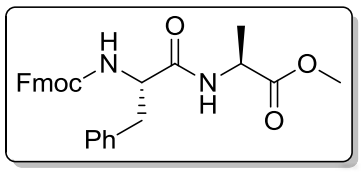
Yield 261 mg, 80%; colorless crystalline solid; R_f = 0.50 (EtOAc:Hexane, 1:4); m.p. 112-115 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26-8.24 (d, *J* = 8.0 Hz, 1H), 7.95-7.90 (m, 1H), 7.89-7.84 (m, 2H), 4.45-4.40 (q, 2H), 1.39-1.36 ppm (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.7, 148.9, 137.0, 133.5, 132.8, 126.6, 125.6, 105.9, 65.0, 14.0 ppm; IR (KBr) 3103, 2988, 2224, 1748, 1544, 928, 742 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{11}H_{10}N_3O_7S$ 328.0239, found 328.0235.

Intermediate V (Scheme 2.3.1): Oxyma ester naphthanoic acid



White solid; R_f = 0.40 (EtOAc:Hexane, 1.0:9.0), ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.13-8.11 (t, *J* = 8.0 Hz, 1H), 8.00-7.98 (d, *J* = 7.8, Hz, 1H), 7.64-7.61 (t, *J* = 8.0 Hz, 2H), 7.64-7.61 (t, *J* = 6.5, Hz, 1H), 7.58-7.56 (t, *J* = 6.6, Hz, 1H), 4.46-4.43 (q, *J* = 6.0 Hz, 2H), 1.43-1.40 ppm (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.9, 157.1, 136.5, 133.1, 132.4, 129.9, 129.7, 129.2, 128.0, 127.4, 125.0, 122.8, 107.2, 64.7, 14.1 ppm; IR (KBr): 2924, 2853, 2224, 1715, 1646, 1593, 1541, 1398, 668, 544 cm^{-1}; HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{16}H_{12}N_2NaO_4$ 319.0695, found 319.0691.

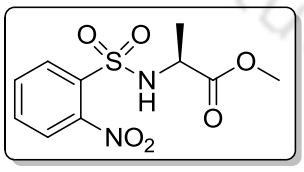
Methyl 2-(2-((((9H-fluoren-9-yl)methoxy) carbonyl)amino)-3-phenylpropanamido) propanoate (coupling by *o*-nitrobenzenesulfonyl chloride)



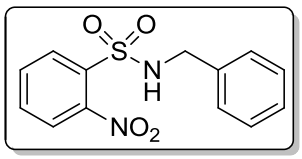
Yield: 307 mg (65%); white solid; R_f = 0.40 (EtOAc:Hexane, 3.0:7.0); m.p.178-180 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09-8.07 (m, 1H), 7.94-7.91 (m, 1H), 7.77-7.72 (m, 2H), 7.55-7.52 (t, *J* = 8.0 Hz, 2H), 7.42-7.38 (t, *J* = 8.0 Hz, 2H), 7.32-7.24 (m, 4H), 7.21-7.19 (m, 1H), 6.33 (br, 1H), 5.39 (br, 1H), 4.52-4.43 (m, 3H), 4.32-4.23 (m, 2H), 4.20-4.17 (t, *J* = 8.0 Hz, 1H), 3.52 (s, 3H), 3.12-3.05 (m, 1H), 1.50-1.48 ppm (d, *J* = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.9, 172.1, 170,67, 156.08, 143.9, 141.4, 136.4, 133.7, 132.9, 130.6, 129.5, 128.5, 127.8, 127.8, 127.2, 125.7, 120.1, 67.2, 56.1, 52.2, 48.3, 47.2, 19.7, 18.3 ppm; IR (KBr): 3304, 1738, 1690, 1652, 1534, 1262, 698 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{28}H_{29}N_2O_5$ 473.2076, found 473.2079.

(L) Methyl 2-(2-nitrophenylsulfonamido)propanoate[105] (coupling by *o*-nitrobenzenesulfonyl chloride)

Pale yellow solid; R_f = 0.50 (EtOAc:Hexane, 3.0:7.0); m.p. 68-70 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29-8.27 (m, 1H), 8.07-8.05 (m, 1H), 7.92-7.90 (m, 1H), 7.74-7.71 (m, 1H), 6.18 (br, 1H), 4.23-4.19 (m, 1H), 3.50 (s, 3H), 1.50-1.48 ppm (d, *J* = 8.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 172.1, 147.9, 134.4, 133.8, 133.0, 130.6, 125.7, 52.7, 48.8, 16.7 ppm; IR (KBr): 3330, 2921, 1746, 1691, 1536, 1261, 1184, 741 cm^{-1}; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{10}H_{12}N_2NaO_6S$ 311.0314, found 311.0317.

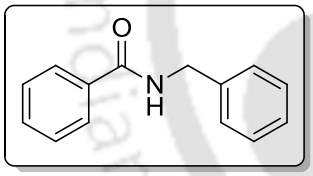


_N_-benzyl-2-nitrobenzenesulfonamide (byproduct of the reaction without pre-activation)



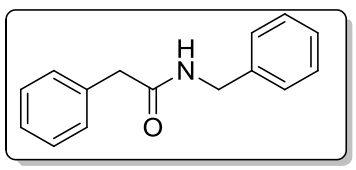
Pale yellow solid; R_f = 0.52 (EtOAc:Hexane, 3.0:7.0); m.p. 42-44 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01-7.98 (m, 1H), 7.83-7.81 (m, 1H), 7.70-7.63 (m, 2H), 7.31-7.22 (m, 5H), 5.77 (br, 1H), 4.33-4.32 ppm (d, *J* = 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.9, 135.8, 134.1, 133.6, 132.9, 131.1, 128.8, 128.0, 125.4, 48.0 ppm; IR (KBr): 3340, 2961, 1691, 1535, 1221, 1182, 933, 742 cm^{-1}; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{13}H_{12}N_2NaO_4S$ 315.0415, found 315.0420.

_N_-benzylbenzamide[106] (entry 1, Table 2.1.2)



Yield: 186 mg (88%); white solid; R_f = 0.50 (EtOAc:Hexane, 2.0:8.0) mp: 102-104 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78-7.76 (m, 2H), 7.42-7.37 (m, 4H), 7.36-7.28 (m, 4H), 4.63-4.62 ppm (d, *J* = 4.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6, 138.4, 134.4, 131.6, 128.8, 128.6, 127.9, 127.5, 127.1, 44.1 ppm; IR (KBr): 3290, 2924, 1637, 1551, 765, 565 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_{14}NO$ 212.1075, found 212.1073.

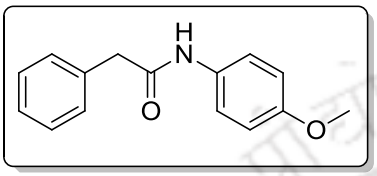
_N_-Benzyl-_2_-phenylacetamide[106] (entry 2, Table 2.1.2)



Yield: 205 mg (91%); white solid; R_f = 0.51 (EtOAc:Hexane, 2.0:8.0); mp: 76-78 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.27 (m, 5H), 7.24-7.16 (m, 5H), 5.76 (br, 1H), 4.42 (s, 2H), 3.62 ppm (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 138.3, 135.0, 129.4, 129.0, 128.7, 127.5, 127.4, 127.3, 43.7, 43.6 ppm; IR (KBr): 3289,

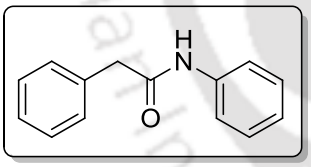
2925, 1638, 1552, 784, 634, 566 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{15}H_{16}NO$ 226.1232, found 226.1231.

_N_-(4-Methoxyphenyl)-2-phenylacetamide (entry 3, Table 2.1.2)



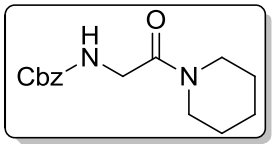
Yield: 198 mg (82%); pale yellowish solid; R_f = 0.40 (EtOAc:Hexane, 3.0:7.0); m.p.121-123°C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.39-7.37 (m, 2H), 7.35-7.29 (m, 5H), 7.12 (br, 1H), 6.81-6.79 (d, *J* = 8.0 Hz, 2H), 3.75 (s, 3H), 3.70 ppm (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 169.3 156.7, 134.7, 130.8, 129.7, 129.3, 127.7, 122.0, 114.2, 55.6, 44.8 ppm; IR (KBr): 3330, 2930, 2832, 1751, 1519, 1262, 1188, 1016, 544 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{15}H_{16}NO_2$ 242.1181, found 242.1183.

2-_N_-Diphenyl-acetamide[107] (entry 4, Table 2.1.2)



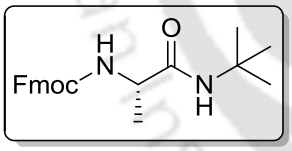
Yield: 181 mg (86%); white solid; R_f = 0.40 (EtOAc:Hexane, 2.0:8.0); mp: 115-117 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42-7.36 (m, 5H), 7.35-7.06 (m, 5H), 3.73 ppm (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 137.9, 134.7, 129.5, 129.1, 128.9, 127.5, 124.5, 120.2, 44.6 ppm; IR (KBr): 3285, 2967, 1657, 1601, 865, 543 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_{14}NO$ 212.1075, found 212.1071.

Benzyl 2-oxo-2-(piperidin-1-yl) ethylcarbamate[108] (entry 5, Table 2.1.2)



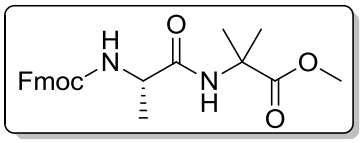
Yield: 265 mg (89%); white solid; R_f = 0.30 (EtOAc:Hexane, 4.0:6.0); mp: 113-116 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.28 (m, 5H), 5.84 (br, 1H), 5.09 (s, 2H), 3.98-3.97 (d, *J* = 4.0 Hz, 2H), 3.54-3.52 (t, *J* = 5.2 Hz, 2H), 3.29-3.27 (t, *J* = 5.2 Hz, 2H), 1.70-1.68 (d, *J* = 4.0 Hz, 2H), 1.63-1.61 (d, *J* = 4.8 Hz, 2H), 1.54-1.52 ppm (d, *J* = 5.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.0, 156.3, 136.6, 128.5, 128.1, 128.0, 66.8, 45.4, 43.1, 42.6, 34.0, 26.2, 25.7, 25.4, 25.0, 24.3 ppm; IR (KBr): 3293, 2936, 1707, 1641, 763, 541 cm^{-1}; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{15}H_{20}N_2NaO_3$ 299.1372, found 299.1368.

(9H-Fluoren-9-yl)methyl (1-(tert-butylamino)-1-oxopropan-2-yl) carbamate (entry 6, Table 2.1.2)



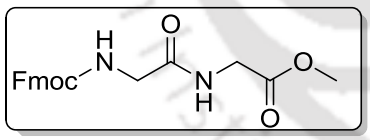
Yield: 296 mg (81%); yellowish solid; R_f = 0.40 (EtOAc:Hexane, 3.0:7.0); $[\alpha]_D^{25}$ = + 4.07 ($CHCl_3$, c = 0.54); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.76-7.75 (d, *J* = 7.8 Hz, 2H), 7.59-7.57 (d, *J* = 8.0 Hz, 2H), 7.41-7.38 (m, 2H), 7.32-7.29 (m, 2H), 4.43-4.37 (m, 3H), 4.24-4.19 (t, *J* = 6.0 Hz, 1H), 4.13 (br, 1H), 1.36-1.35 (d, *J* = 6.0 Hz, 3H), 1.34 ppm (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 171.6, 156.1, 144.0, 141.5, 127.9, 127.2, 125.2, 120.1, 67.2 51.5, 47.3, 28.8, 19.1 ppm; IR (KBr): 3330, 3231, 2984, 1754, 1243, 752, 542 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{22}H_{27}N_2O_3$ 367.2022, found 367.2025.

(L) Methyl 2-(2-((((9H-fluoren-9-yl)methoxy) carbonyl)amino) propanamido)-2-methylpropanoate (entry 7, Table 2.1.2)



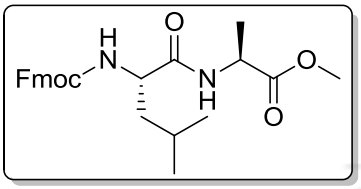
Yield: 328 mg (80%); white solid; R_f = 0.50 (EtOAc:Hexane, 3.0:7.0); mp: 86-88 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77-7.75 (d, *J* = 8.0 Hz, 2H), 7.62-7.58 (m, 2H), 7.42-7.38 (t, *J* = 8.0 Hz, 2H), 7.32-7.29 (t, *J* = 7.8 Hz, 2H), 5.42 (br, 1H), 4.43-4.37 (m, 2H), 4.24-4.21 (t, *J* = 8.0 Hz, 1H), 4.16-4.10 (m, 1H), 3.76 (s, 3H), 1.44-1.42 (d, *J* = 12.0 Hz, 3H), 1.25 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.7, 155.8, 144.1, 141.5, 127.9, 127.2, 125.2, 124.9, 120.2, 76.9, 67.2, 52.7, 50.5, 49.8, 47.3, 29.7, 18.9 ppm; IR (KBr): 3341, 1722, 1654, 1650, 1231, 664 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{23}H_{27}N_2O_5$ 411.1920, found 411.1922.

Methyl 2-(2-(((9H-fluoren-9-yl) methoxy)carbonyl) acetamido)acetate (entry 8, Table 2.1.2)



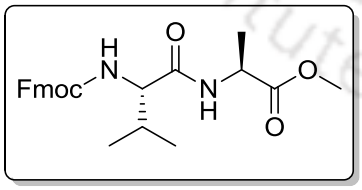
Yield: 321 mg (91%); white solid; R_f = 0.31 (EtOAc:Hexane, 4.0:6.0); mp: 162-163 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76-7.74 (d, *J*= 8.0 Hz, 2H), 7.58-7.56 (d, *J* = 8.0 Hz, 2H), 7.40-7.37 (t, *J*= 8.0 Hz, 2H), 7.31-7.27 (t, *J* = 8.0 Hz, 2H), 6.80 (br, 1H), 5.73 (br, 1H), 4.43-4.41 (d, *J* = 6.8 Hz, 2H), 4.22-4.19 (t, *J* = 7.2 Hz, 1H), 4.04-4.03 (d, *J* = 8.0 Hz, 2H), 3.92-3.91 (d, *J* = 6.8 Hz, 2H), 3.73 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 169.7, 156.8, 143.7, 141.2, 128.6, 128.5, 128.3, 127.1, 67.1, 47.0, 44.2, 41.2, 33.8 ppm; IR (KBr): 3316, 2931, 1734, 1692, 1654, 865, 523 cm^{-1}; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{20}H_{19}NNaO_5$ 376.1161, found 376.1165.

(L,L) Methyl 2-(2-(((9H-fluoren-9-yl)methoxy)carbonyl)-4-methylpentanamido) propanoate (entry 9, Table 2.1.2)



Yield: 390 mg (89%); white solid; R_f = 0.50 (EtOAc:Hexane, 3.0:7.0); mp: 161-163 °C; $[\alpha]_D^{25}$ = - 16.5 ($CHCl_3$, c = 0.35); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76-7.74 (d, *J* = 8.0 Hz, 2H), 7.59-7.57 (d, *J* = 8.0 Hz, 2H), 7.41-7.37 (t, *J* = 7.2 Hz, 2H), 7.32-7.28 (t, *J* = 7.2 Hz, 2H), 6.62 (br, 1H), 5.36-5.34 (d, *J* = 8.0 Hz, 1H), 4.58-4.52 (m, 1H), 4.41-4.35 (m, 1H), 4.22-4.19 (t, *J* = 6.4 Hz, 3H), 3.73 (s, 3H), 1.81-1.74 (m, 1H), 1.65-1.63 (m, 2H), 1.40-1.38 (d, *J* = 6.8 Hz, 3H), 1.01-0.98 ppm (d, *J* = 6.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.2, 163.1, 156.6, 143.8, 141.1, 129.3, 128.6, 127.5, 126.9, 124.9, 66.6, 57.4, 52.2, 46.9, 38.2, 38.3, 28.1, 18.0 ppm; IR (KBr): 3307, 2925, 1754, 1694, 1654, 879, 534 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{25}H_{31}N_2O_5$ 439.2233, found 439.2235.

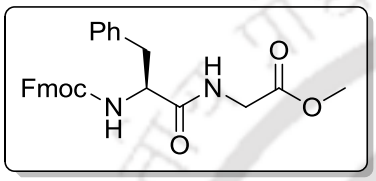
(L,L) Methyl 2-(2-(((9H-fluoren-9-yl)methoxy)carbonyl)-3-methylbutanamido) propanoate[109] (entry 10, Table 2.1.2)



Yield: 369 mg (87%); white solid; R_f = 0.50 (EtOAc:Hexane, 3.0:7.0); mp: 204-205 °C; $[\alpha]_D^{25}$ = - 14.5 ($CHCl_3$, c = 0.40); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76-7.75 (d, *J* = 8.0 Hz, 2H), 7.60-7.58 (d, *J* = 8.0 Hz, 2H), 7.41-7.37 (t, *J* = 8.0 Hz, 2H), 7.31-7.28 (t, *J* = 8.0 Hz, 2H), 6.54-6.52 (d, *J* = 8.0 Hz, 1H), 5.54-5.52 (d, *J* = 8.0 Hz, 1H), 4.60-4.58 (d, *J* = 8.0 Hz, 2H), 4.44-4.35 (m, 1H), 4.23-4.21 (d, *J* = 8.0 Hz, 1H) 4.04-4.00 (t, *J* = 7.0 Hz, 1H), 3.73 (s, 3H), 2.11-2.08 (m, 1H), 1.41-1.39 (d, *J* = 8.0 Hz, 3H), 0.98-0.96 ppm (d, *J* = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.3, 171.2, 156.6, 144.0,

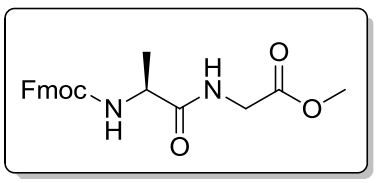
141.4, 127.8, 127.2, 125.2, 120.1, 67.2, 60.4, 52.6, 48.2, 47.3, 31.9, 29.8, 19.2, 18.2 ppm; IR (KBr): 3296, 2953, 1745, 1692, 1650, 765, 599 cm^{-1}; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{24}H_{28}N_2NaO_5$ 447.1896, found 447.1901.

(L) Methyl 2-(2-(((9H-fluoren-9-yl)methoxy)carbonyl)-3-phenylpropanamido) acetate (entry 11, Table 2.1.2)



Yield: 412 mg (93%); white solid; R_f = 0.52 (EtOAc:Hexane, 3.0:7.0); mp: 175-178 °C; $[\alpha]_D^{25}$ = -6.5 ($CHCl_3$, c = 0.60); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77-7.75 (d, *J* = 8.0 Hz, 4H), 7.54-7.50 (t, *J* = 8.0 Hz, 2H), 7.42-7.38 (t, *J* = 8.0 Hz, 2H), 7.32-7.28 (m, 5H), 6.31 (br, 1H), 5.33 (br, 1H), 4.45-4.40 (t, *J* = 8.0 Hz, 2H), 4.40-4.32 (d, *J* = 8.0 Hz, 1H), 4.20-4.16 (t, *J* = 7.2 Hz, 1H), 4.00-3.99 (d, *J* = 4.0 Hz, 2H) 3.72 (s, 3H); 3.10-3.00 ppm (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 171.5, 170.0, 156.2, 143.8, 141.4, 136.5, 129.4, 128.8, 128.5, 127.8, 127.7, 127.3, 127.2, 125.1, 120.1, 67.2, 56.1, 52.5, 47.2, 41.3, 38.5 ppm; IR (KBr): 3300, 1749, 1692, 1651, 1539, 1260, 757; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{27}H_{26}NO_5$ 444.1811, found 444.1809.

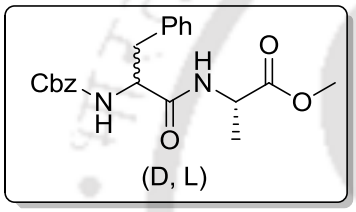
(L) Methyl 2-(2-(((9H-fluoren-9-yl)methoxy)carbonyl) propanamido)acetate (entry 12, Table 2.1.2)



Yield: 319 mg (87%); white solid; R_f = 0.40 (EtOAc:Hexane, 4.0:6.0); mp: 157-159 °C; $[\alpha]_D^{25}$ = -12.4 ($CHCl_3$, c = 0.60); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75-7.73 (d, *J* = 8.0 Hz, 2H), 7.56-7.55 (d, *J* = 8.0 Hz, 2H), 7.39-7.35 (t, *J* = 8.0 Hz, 2H), 7.30-7.27 (t, *J* = 8.0 Hz, 2H), 6.63 (br, 1H), 5.54 (br, 1H), 4.39-4.38 (t, *J* = 4.0 Hz, 2H),

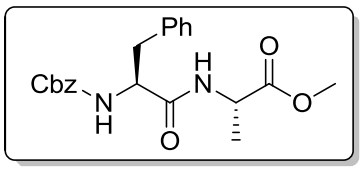
4.31-4.30 (t, *J* = 4.0 Hz, 1H), 4.20-4.17 (d, *J* = 4.0 Hz, 1H), 4.01-3.99 (d, *J* = 4.0 Hz, 2H), 3.71 (s, 3H), 1.40-1.38 ppm (d, *J* = 8.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 172.9, 170.2, 156.2, 143.9, 141.4, 127.8, 127.2, 125.2, 120.1, 67.2, 52.5, 50.5, 47.2, 41.3, 18.7 ppm; IR (KBr): 3294, 1731, 1693, 1648, 1551, 1265, 758 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{21}H_{23}N_2O_5$ 383.1607, found 383.1609.

(DL) Methyl 2-(2-(benzyloxycarbonyl)-3-phenyl propanamido)propanoate[110] (entry 13, Table 2.1.2)



Yield: 345 mg (90%); white solid; R_f = 0.51 (EtOAc:Hexane, 3.0:7.0); mp: 120-122 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.30 (m, 4H), 7.29-7.26 (m, 4H), 7.23-7.17 (m, 2H), 6.60 (br, 1H), 5.53 (br, 1H), 5.05 (s, 2H), 4.53-4.51 (d, *J* = 8.0 Hz, 1H), 4.47-4.45 (d, *J* = 8.0 Hz, 1H), 3.67 (s, 3H), 3.07-3.05 (d, *J* = 8.0 Hz, 2H), 1.32-1.30 (d, *J* =8.0 Hz, 3H), 1.21-1.19 ppm (d, *J* = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0, 172.9, 170.9, 170.7, 156.1, 136.6, 136.3, 129.3, 128.4, 128.1, 127.9, 126.9, 66.9, 56.1, 52.4, 38.9, 38.6, 17.8 ppm; IR (KBr): 3305, 1737, 1690, 1652, 1537, 1262, 698 cm^{-1}; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{21}H_{24}N_2NaO_5$ 407.1583, found 407.1588.

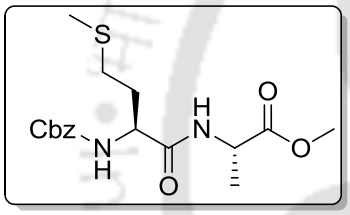
(L) Methyl 2-(2-(benzyloxycarbonyl)-3-phenyl propanamido)propanoate[110] (entry 14, Table 2.1.2)



Yield: 349 mg (91%); white solid; R_f = 0.51 (EtOAc:Hexane, 3.0:7.0); mp: 120-122 °C. $[\alpha]_D^{25}$ = - 12.1 ($CHCl_3$, c = 0.32); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-

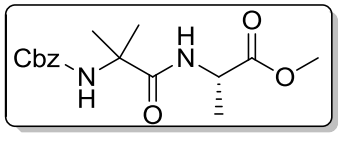
7.31 (m, 4H), 7.30-7.24 (m, 4H), 7.22-7.17 (m, 2H), 6.47 (br, 1H), 5.42 (br, 1H), 5.07 (s, 2H), 4.51-4.52 (d, *J* = 4.0 Hz, 1H), 4.48-4.46 (d, *J* = 8.0 Hz, 1H), 3.70 (s, 3H), 3.07-3.05 (d, *J* = 8.0 Hz, 2H), 1.32-1.31 ppm (d, *J* =4.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 173.0, 170.7, 156.2, 136.4, 129.5, 128.8, 128.7, 128.6, 128.3, 128.2, 127.2, 67.2, 56.2, 52.6, 49.3, 48.12, 38.7, 18.4 ppm; IR (KBr): 3305, 1737, 1690, 1652, 1537, 1262, 698 cm^{-1}; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{21}H_{24}N_2NaO_5$ 407.1583, found 407.1587.

(L, L) Methyl 2-(2-(benzyloxycarbonyl)-4-(methylthio) butanamido)propanoate (entry 15, Table 2.1.2)



Yield: 327 mg (89%); white solid; R_f = 0.40 (EtOAc:Hexane, 3.0:7.0); mp: 107-110 °C. $[\alpha]_D^{25}$ = + 6.8 ($CHCl_3$, c = 0.70); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.32 (m, 3H), 7.30-7.27 (m, 2H), 6.69 (br, 1H), 5.55 (br, 1H), 5.08 (s, 2H), 4.55-4.52 (t, *J* = 8.0 Hz, 1H), 4.39-4.37 (t, *J* = 8.0 Hz, 1H), 3.71 (s, 3H), 2.59-2.56 (t, *J* = 8.0 Hz, 2H), 2.08 (s, 3H), 2.00-1.94 (q, *J* = 8.0 Hz, 2H), 1.38-1.37 ppm (d, *J* =4.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 173.1, 170.8, 156.1, 136.3, 128.7, 128.4, 128.3, 67.3, 54.0, 527, 48.3, 31.9, 30.0, 18.3, 15.4 ppm; IR (KBr): 3299, 1735, 1688, 1647, 1538, 1265, 697 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{17}H_{25}N_2O_5S$ 369.1484, found 369.1489.

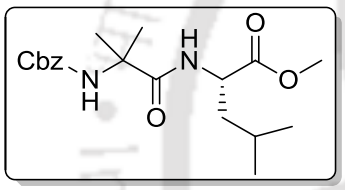
(L) Methyl 2-(2-(benzyloxycarbonyl)-2-methyl propanamido)propanoate (entry 16, Table 2.1.2)



Yield: 260 mg (81%); yellowish solid; R_f = 0.50 (EtOAc:Hexane, 2.0:8.0); mp: 67-70 °C; $[\alpha]_D^{25}$ = - 1.8

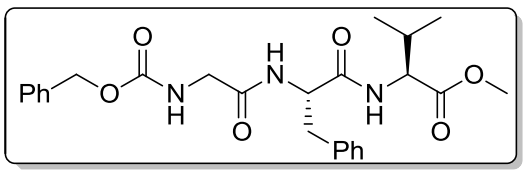
($CHCl_3$, c = 0.70); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.28-7.22 (m, 3H), 7.21-7.15 (m, 2H), 6.89 (br, 1H), 5.82-5.76 (t, *J* = 8.0 Hz, 1H), 4.98 (s, 2H), 4.43 (br, 1H), 3.58 (s, 3H), 1.32 (s, 6H), 1.17-1.14 ppm (d, *J* =4.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 174.2, 173.5, 155.1, 136.4, 128.5, 128.1, 128.0, 66.6, 56.8, 52.4, 48.2, 25.1, 25.1, 18.0 ppm; IR (KBr): 3316, 1734, 1692, 1654, 1234, 674 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{16}H_{23}N_2O_5$ 323.1607, found 323.1610.

(L) Methyl 2-(2-(benzyloxycarbonyl)-2-methyl propanamido)-4-methylpentanoate (entry 17, Table 2.1.2)



Yield: 283 mg (78%); white solid; R_f = 0.50 (EtOAc:Hexane, 2.0:8.0); mp: 77-80 °C; $[\alpha]_D^{25}$ = - 1.5 ($CHCl_3$, c = 1.64); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.35-7.32 (m, 3H), 7.31-7.26 (m, 2H), 6.70 (br, 1H), 5.31 (br, 1H), 5.09 (s, 2H), 4.60-4.58 (t, *J* = 4.0 Hz, 1H), 3.71 (s, 3H), 1.65-1.61 (m, 3H), 1.50 (s, 3H), 1.49 (s, 3H), 0.95-0.92 ppm (d, *J* = 4.0 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 174.3, 173.6, 155.3, 136.4, 128.7, 128.6, 128.9, 66.9, 57.2, 52.39, 51.9, 41.6, 25.9, 25.2, 25.0, 22.9, 22.0 ppm; IR (KBr): 3346, 1723, 1653, 1653, 1235, 664 cm^1; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{19}H_{29}N_2O_5$ 365.2076, found 365.2080.

(L,L) 2-[2-(2-Benzyloxycarbonylamino-acetylamino)-3-phenyl-propionylamino]-3-methyl-butyric acid methyl ester[110] (entry 18, Table 2.1.2)



Yield: 426 mg (91%); white solid; R_f = 0.31 (EtOAc:Hexane, 3.0:7.0); mp 101-103 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.35-7.27 (m,

5H), 7.23-7.11 (m, 5H), 5.88 (br, 1H), 5.11 (s, 2H), 4.78 (br, 1H), 443-4.40 (m, 2H), 3.88-3.84 (m, 2H), 3.60 (s, 3H), 304-299 (m, 2H), 2.06-2.03 (m, 1H), 0.87-0.84 ppm (d, J = 8.0 Hz, 3H), 0.82-0.79 (d, J = 8.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 171.9, 171.4, 169.6, 156.7, 136.5, 136.4, 129.4, 129.0, 128.7, 128.6, 128.5, 128.1, 128.0, 126.8, 67.0, 57.5, 54.5, 52.0, 44.2, 38.5, 31.1, 18.8, 17.9 ppm; IR (KBr): 3406, 1728, 1677, 1651, 1646, 763, 543 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{25}H_{32}N_3O_6$ 470.2291, found 470.2294.

2.8. Selected spectra and chromatograms

2.8.1. ^{1}H NMR and ^{13}C NMR of selected compounds

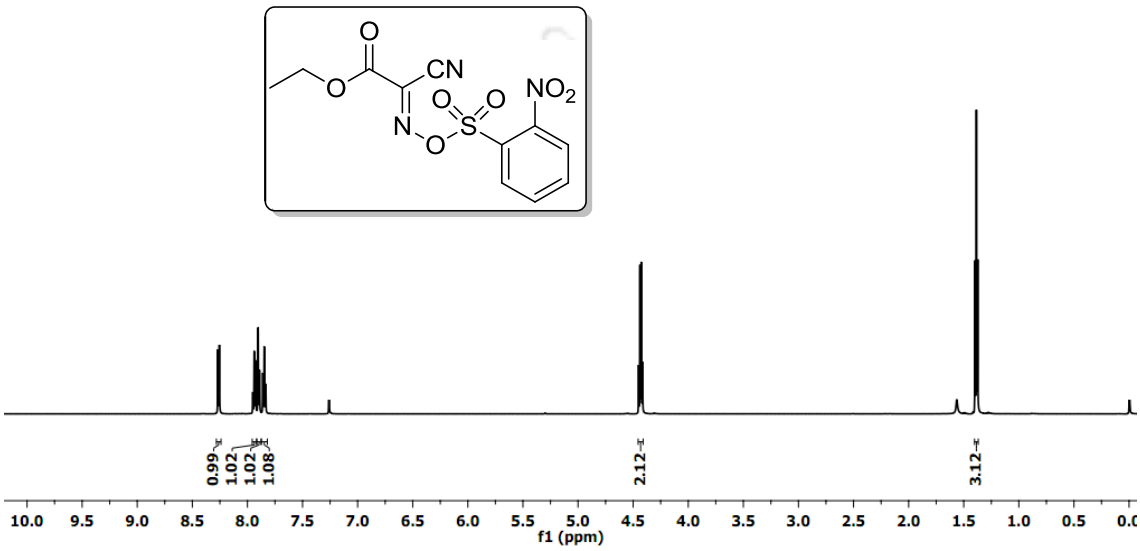


Figure S1: ^{1}H-NMR spectrum of coupling reagent (*o*-NosylOXY, **I**)

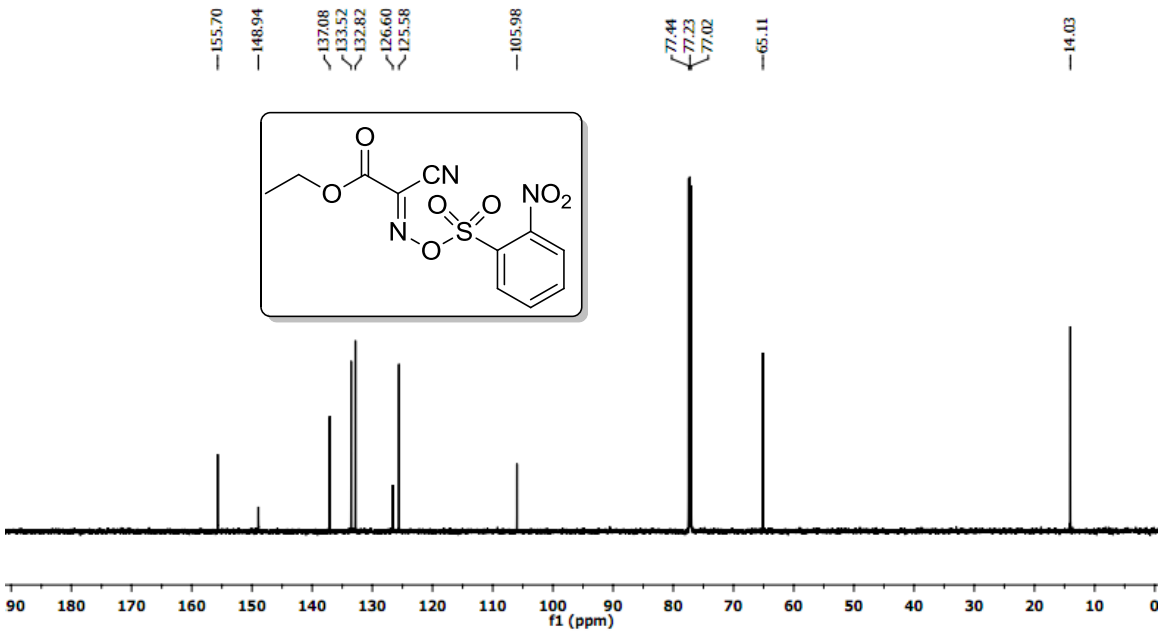


Figure S2: ^{13}C-NMR spectrum of coupling reagent (*o*-NosylOXY, **I**)

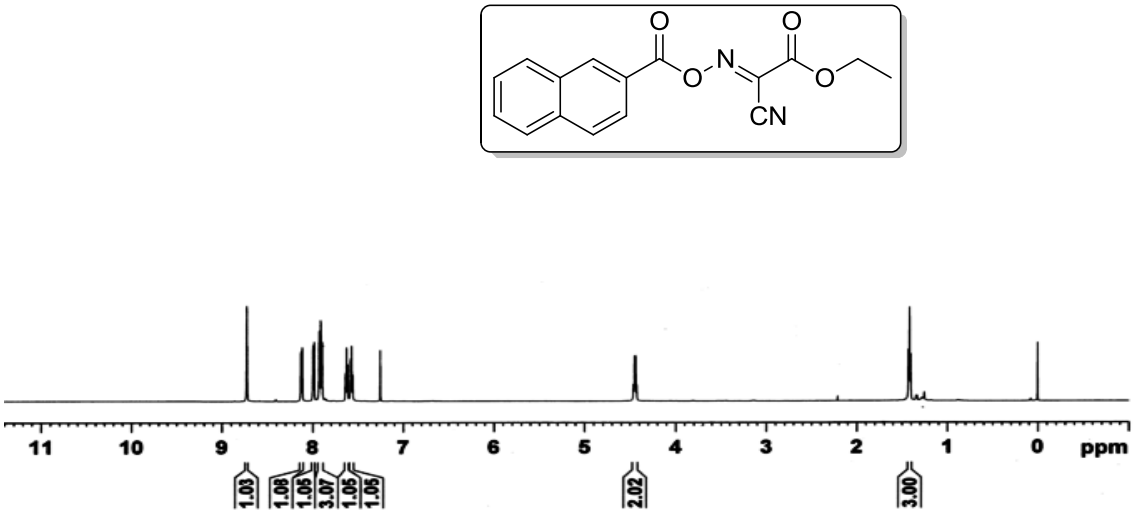


Figure S3: ^{1}H-NMR spectrum of Oxyma ester naphthanoic acid (Intermediate V in Scheme 2.3.1)

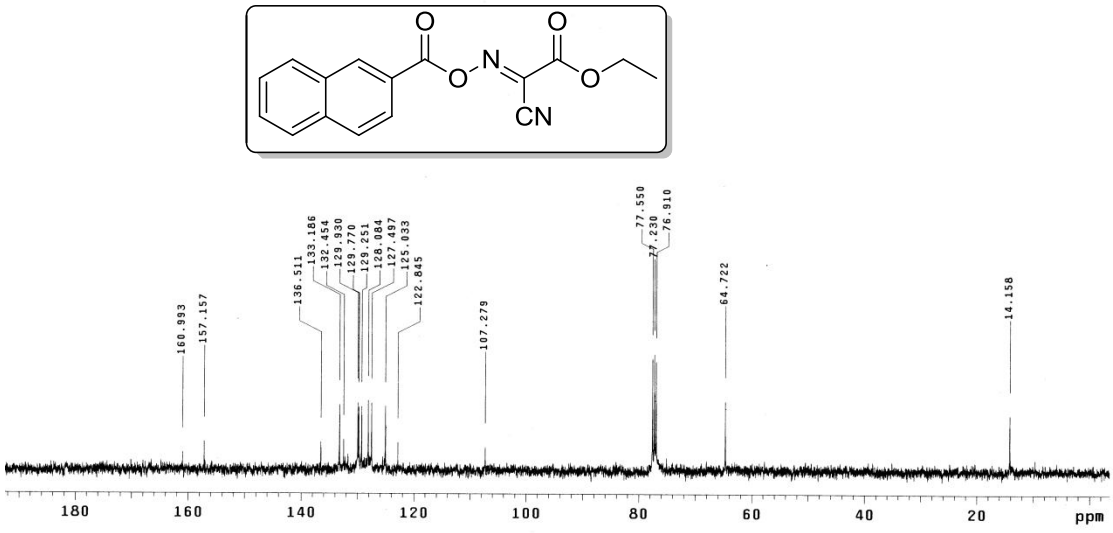


Figure S4: ^{13}C-NMR spectrum of Oxyma ester naphthanoic acid (Intermediate V in Scheme 2.3.1)

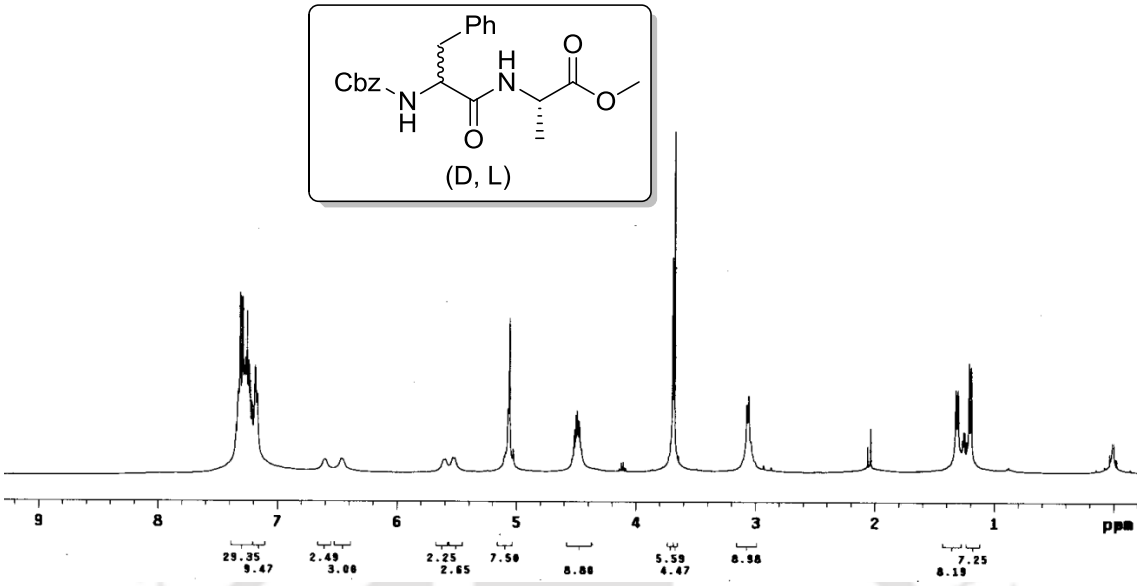


Figure S5: ^{1}H-NMR spectrum of (DL) methyl 2-(2-(benzyloxycarbonyl)-3-phenylpropanamido) propanoate (entry 13, Table 2.1.2)

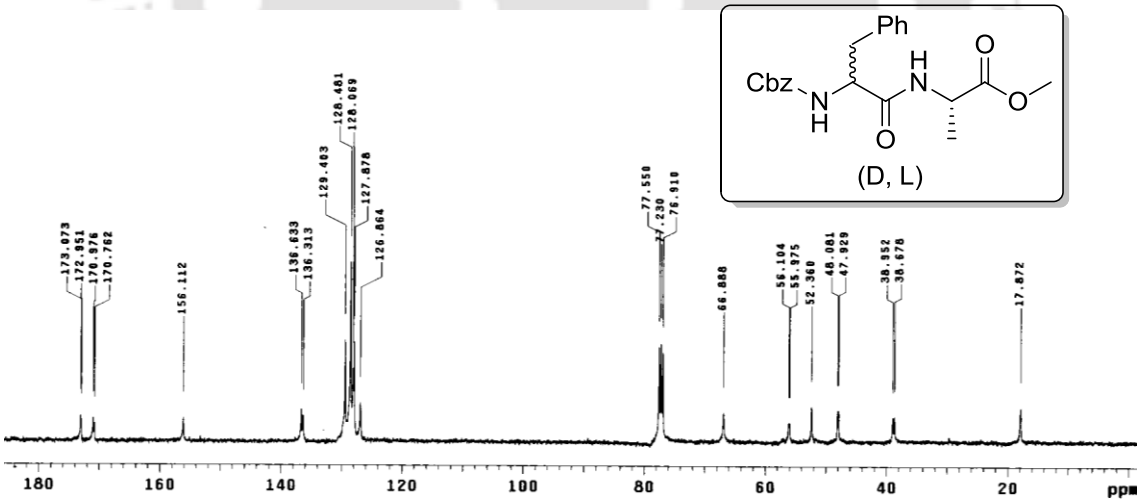


Figure S6: ^{13}C-NMR spectrum of (DL) methyl 2-(2-(benzyloxycarbonyl)-3-phenylpropanamido) propanoate (entry 13, Table 2.1.2)

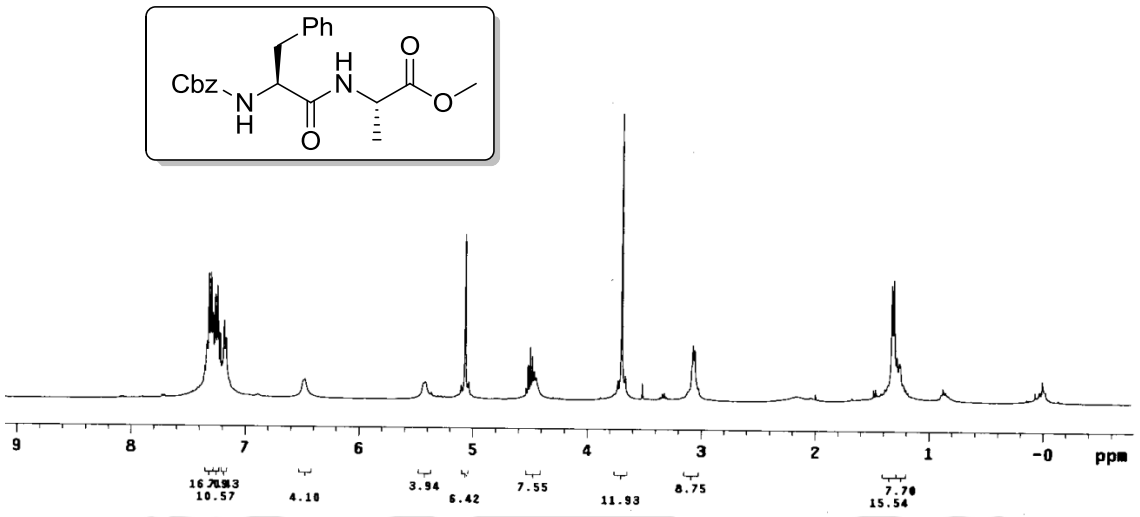


Figure S7: ^{1}H-NMR spectrum of (L) methyl 2-(2-(benzyloxycarbonyl)-3-phenylpropanamido)propanoate (entry 14, Table 2.1.2)

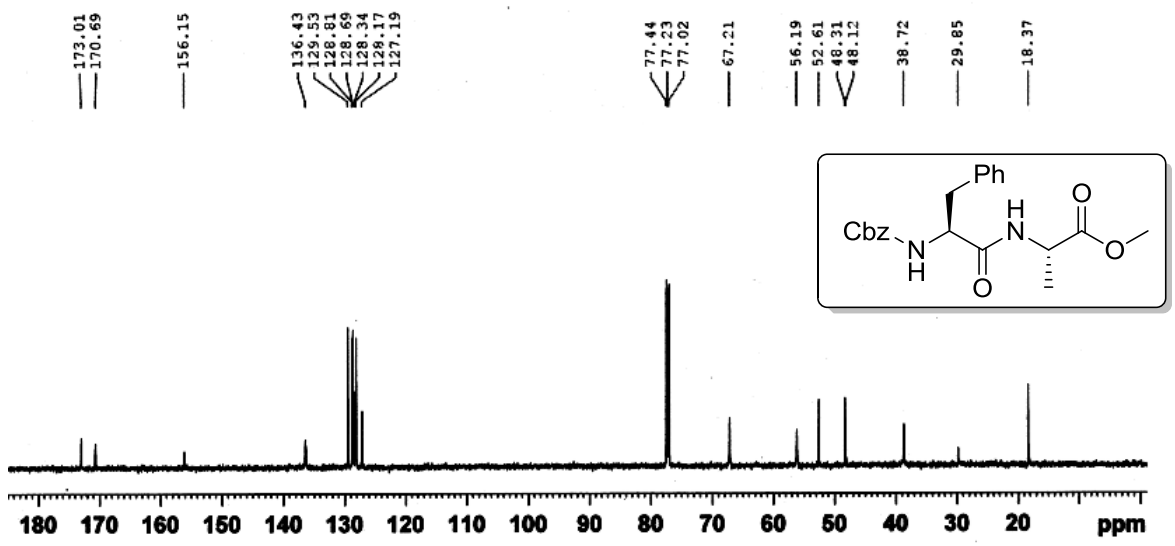


Figure S8: ^{13}C-NMR spectrum of (L) methyl 2-(2-(benzyloxycarbonyl)-3-phenylpropanamido)propanoate (entry 14, Table 2.1.2)

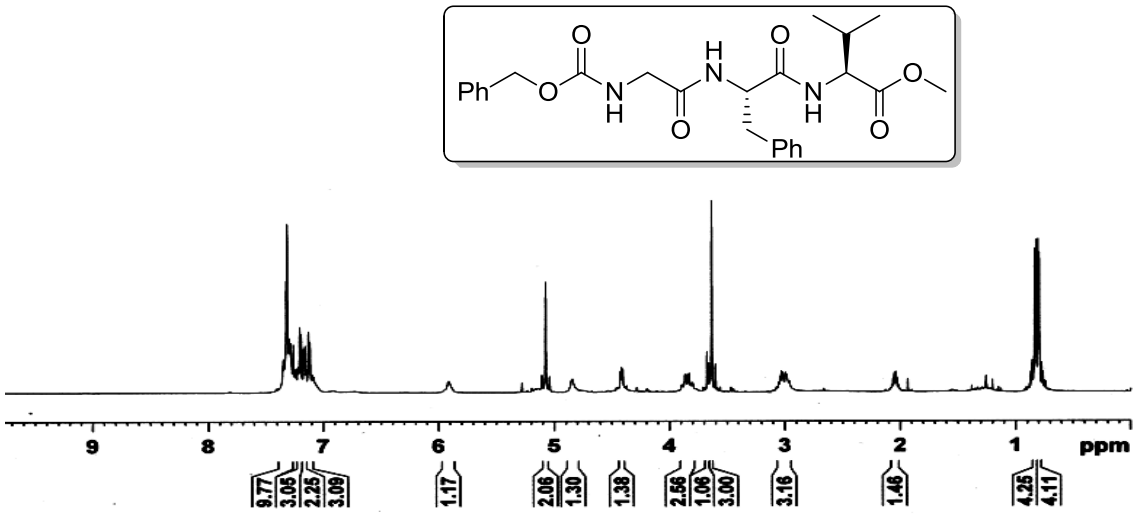


Figure S9: [1]H-NMR spectrum of 2-[2-(2-Benzyloxycarbonylamino-acetylamino)-3-phenylpropionyl amino]-3-methyl-butyric acid methyl ester (entry 18, Table 2.1.2)

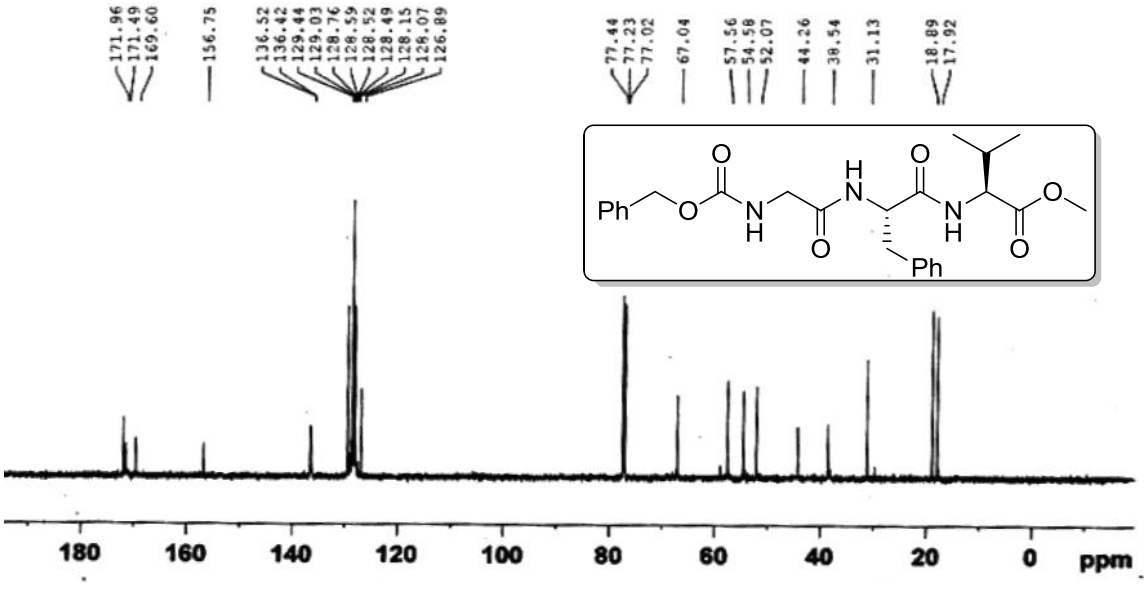


Figure S10: [13]C-NMR spectrum of 2-[2-(2-Benzyloxycarbonylamino-acetylamino)-3-phenyl-propionyl amino]-3-methyl-butyric acid methyl ester (entry 18, Table 2.1.2)

2.8.2. Data for racemization test

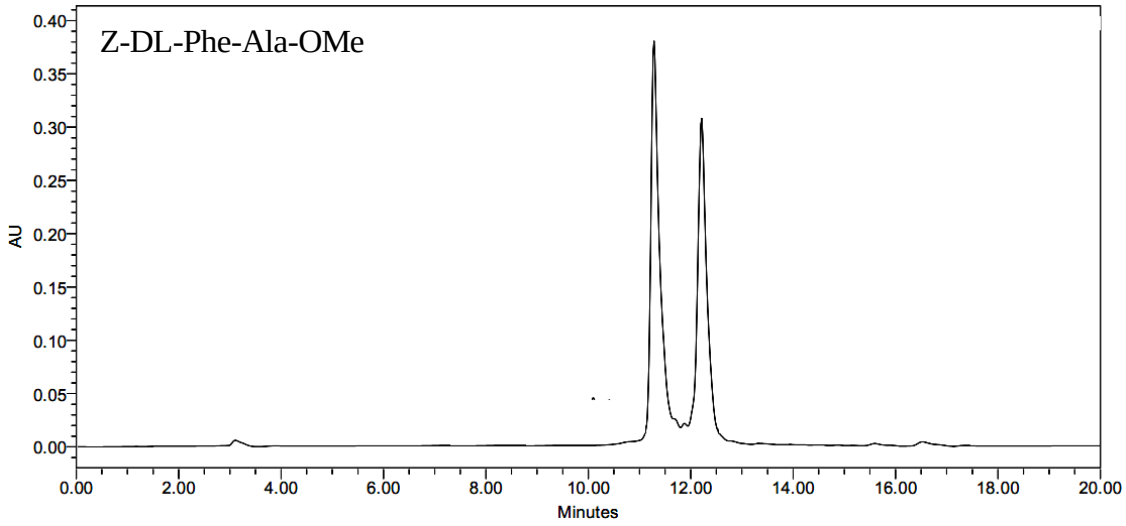


Figure S11: HPLC chromatogram of Z-DL-Phe-Ala-OMe dipeptide run upto 20 min.in Ascentis C18 reverse phase analytical (5 µm, 25 cm× 4.6 mm,) column linear gradient of 0-80%, 0-7 min. then 80-100% upto 20 min., CH_3CN in H_2O with 0.1% formic acid (entry 13, Table 2.1.2)

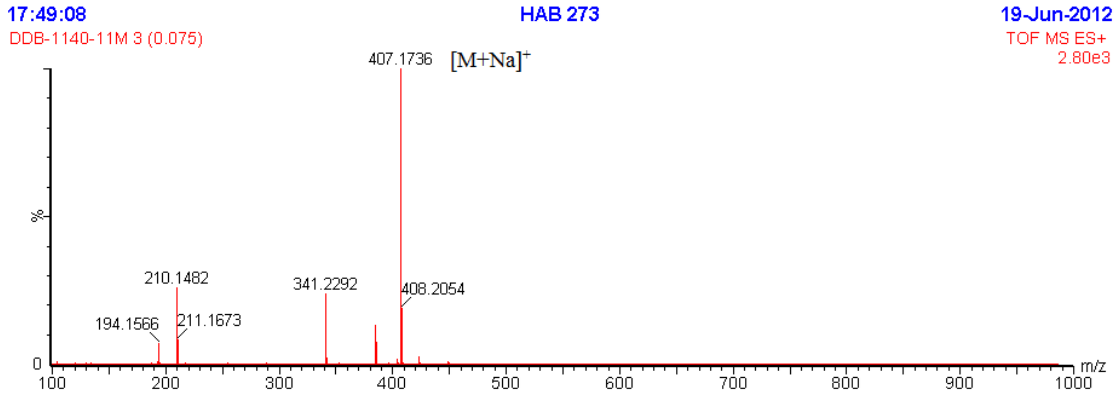


Figure S12: ESI-MS spectrum of Z-DL-Phe-Ala-OMe dipeptide, peak retention time 11.78 min of above chromatogram (entry 13, Table 2.1.2)

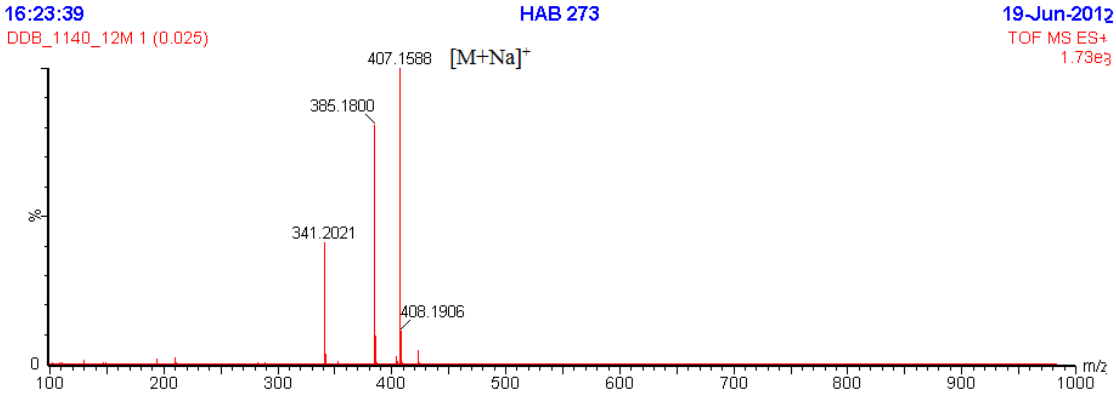


Figure S13: ESI-MS spectrum of Z-DL-Phe-Ala-OMe dipeptide, peak retention time 12.16 min of above chromatogram (entry 13, Table 2.1.2)

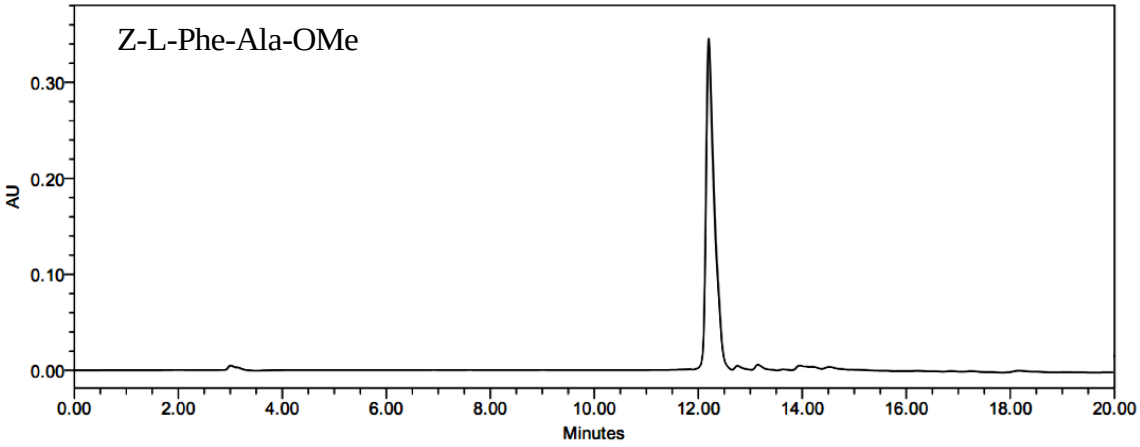


Figure S14: HPLC chromatogram of Z-L-Phe-Ala-OMe dipeptide run in Ascentis C18 reverse phase analytical (5 µm, 25 cm× 4.6 mm,) column linear gradient of 0-80%, 0-7 min. then 80-100 % upto 20 min., CH_3CN in H_2O with 0.1% formic acid (entry 14, Table 2.1.2)

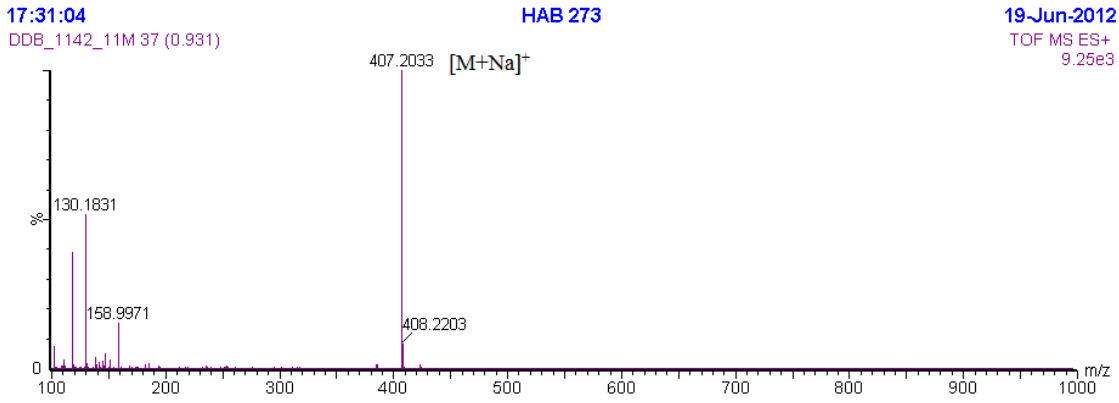


Figure S15: ESI-MS spectrum of Z-L-Phe-Ala-OMe dipeptide, peak retention time 11.76 min of above chromatogram (entry 14, Table 2.1.2)

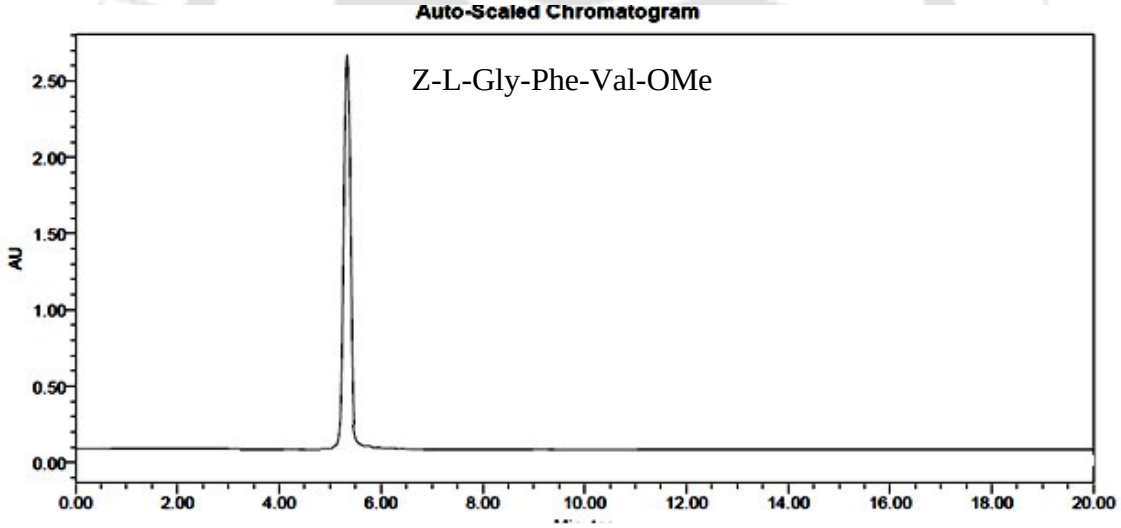


Figure S16: HPLC chromatogram of Z-Gly-Phe-Val-OMe run upto 20 min. in a symmetry C8 (5 µm, 3.5 × 150 mm) column, isocratic gradient 35% acetonitrile in water (entry 18, Table 2.1.2)

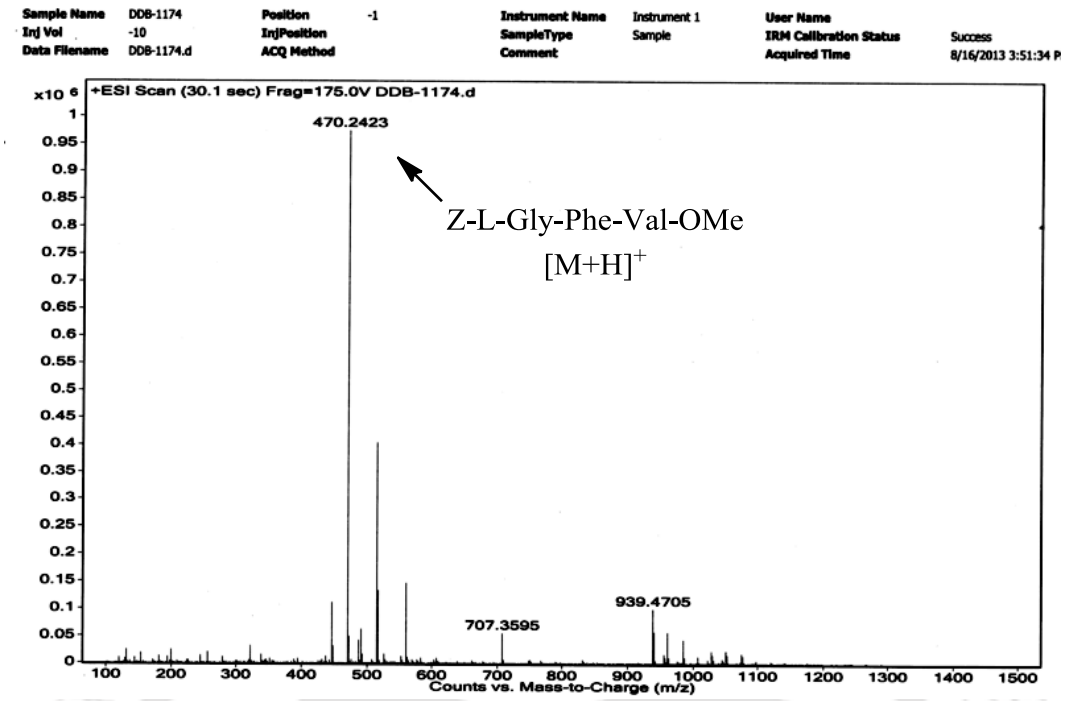


Figure S17: ESI-MS spectrum of Z-Gly-Phe-Val-OMe peptide, peak of above chromatogram (entry 18, Table 2.1.2)

2.8.3. HPLC chromatogram and mass spectrum of Boc-VVIA-OMe

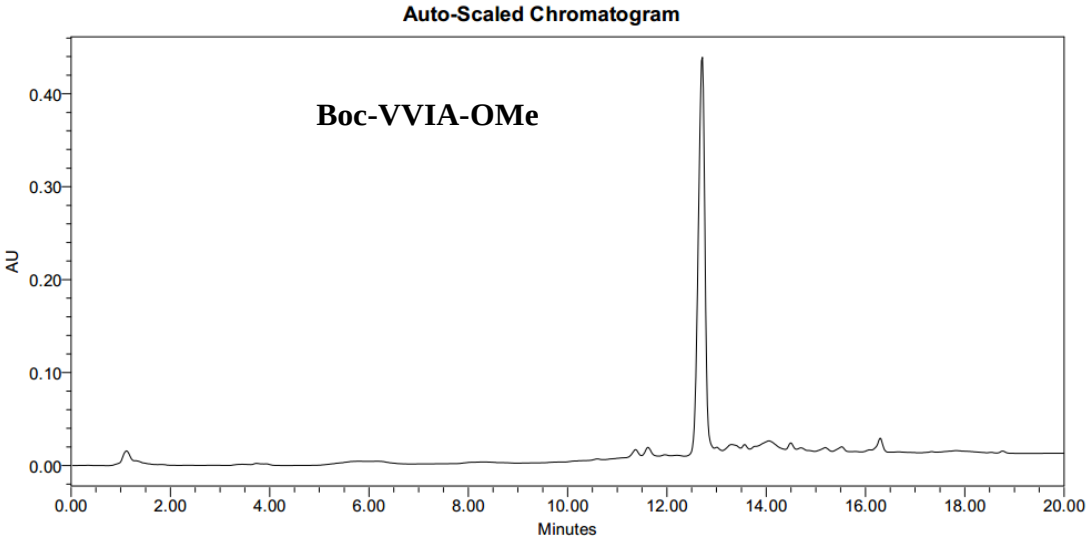


Figure S18: HPLC chromatogram of Boc-VVIA-OMe C8 analytical column (0-20min. linear gradient, 20-100% acetonitrile in water) (product of scheme 2.1.3)

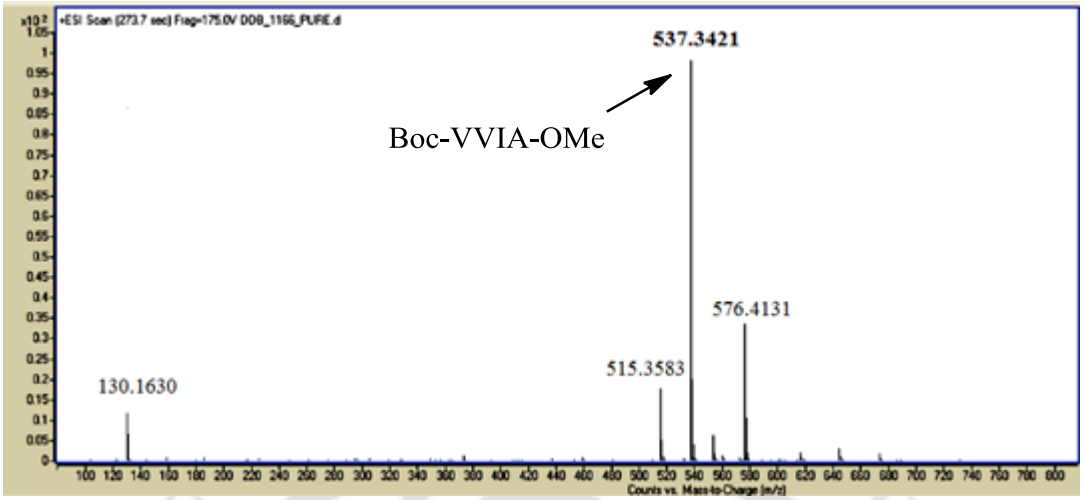


Figure S19: ESI-MS spectrum of Boc-VVIA-OMe peptide, peak of above chromatogram (product of scheme 2.1.3)

2.8.4. HPLC chromatogram and mass spectrum of reaction was performed with *o*-nitrobenenesulfonyl chloride

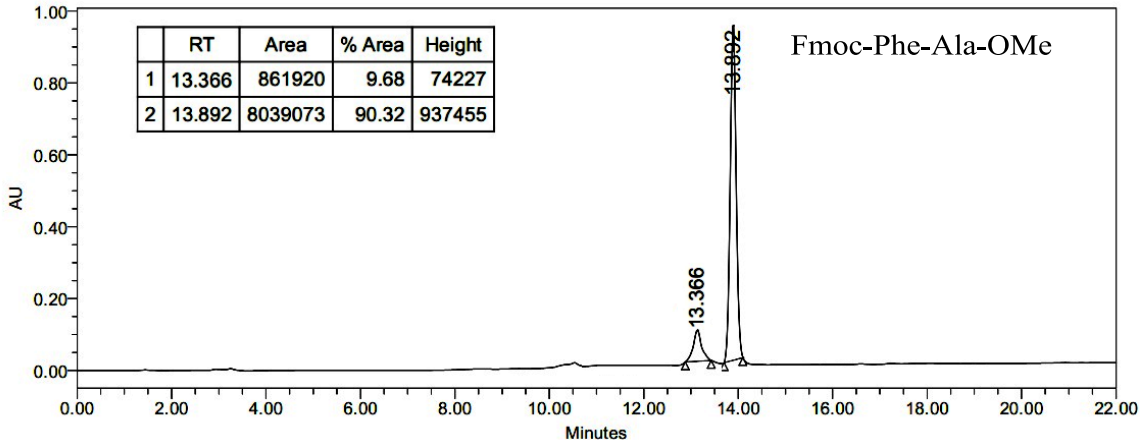


Figure S20: HPLC chromatogram of Fmoc-Phe-Ala-OMe dipeptide run in Ascentis C18 reverse phase analytical column (5 µm, 4.6 mm × 25 cm), linear gradient of 0-80%, 0-7 min. then 80-100% up to 22 min., CH_3CN in H_2O with 0.1% formic acid (Reaction was performed with *o*-nitrobenenesulfonyl chloride)

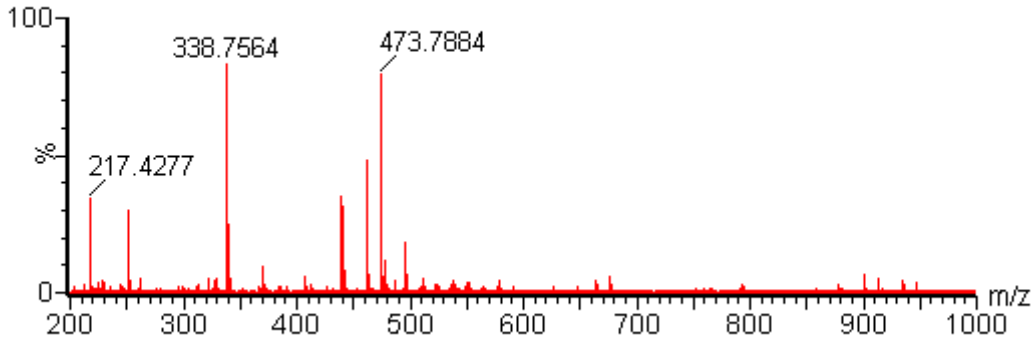


Figure S21: ESI-MS-spectrum of Fmoc-Phe-Ala-OMe dipeptide, Rt, 13.892 min (reaction was performed with *o*-nitrobenenesulfonyl chloride).

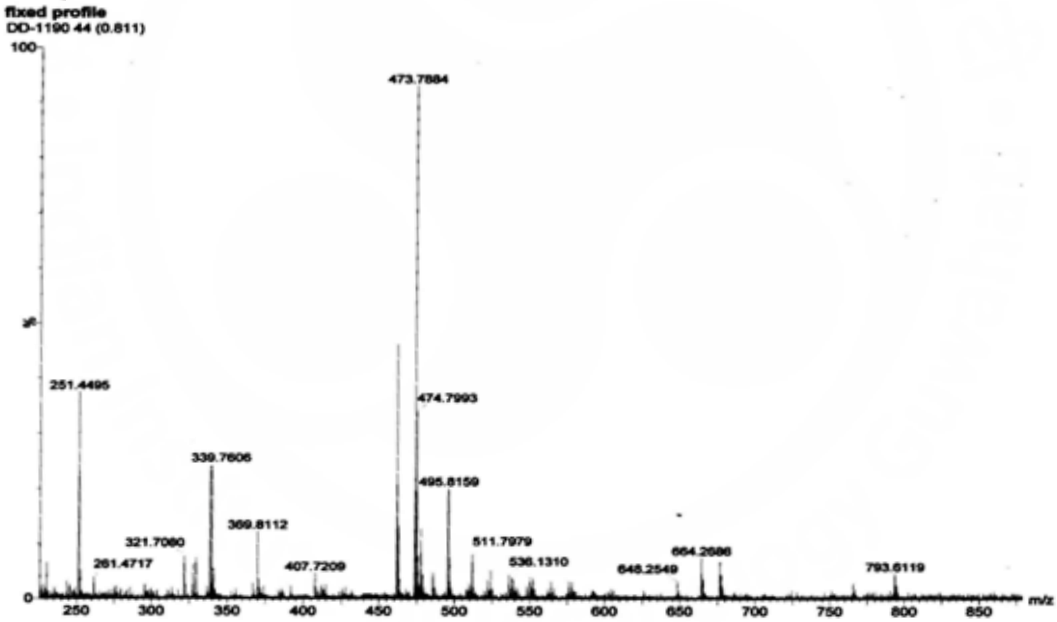


Figure S22: ESI-MS-spectra of Fmoc-Phe-Ala-OMe dipeptide, Rt 13.366 min (reaction was performed with *o*-nitrobenenesulfonyl chloride).

2.8.5. HPLC chromatogram and mass spectrum of oligopeptides

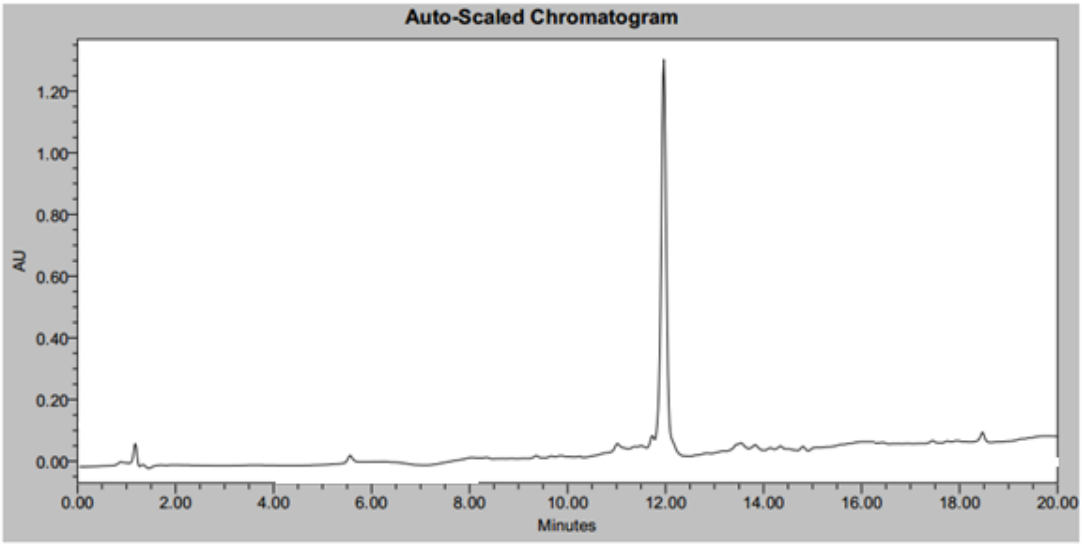


Figure S23: HPLC chromatogram of crude NFGAIILG-NH_2 (Figure 2.1.2a).

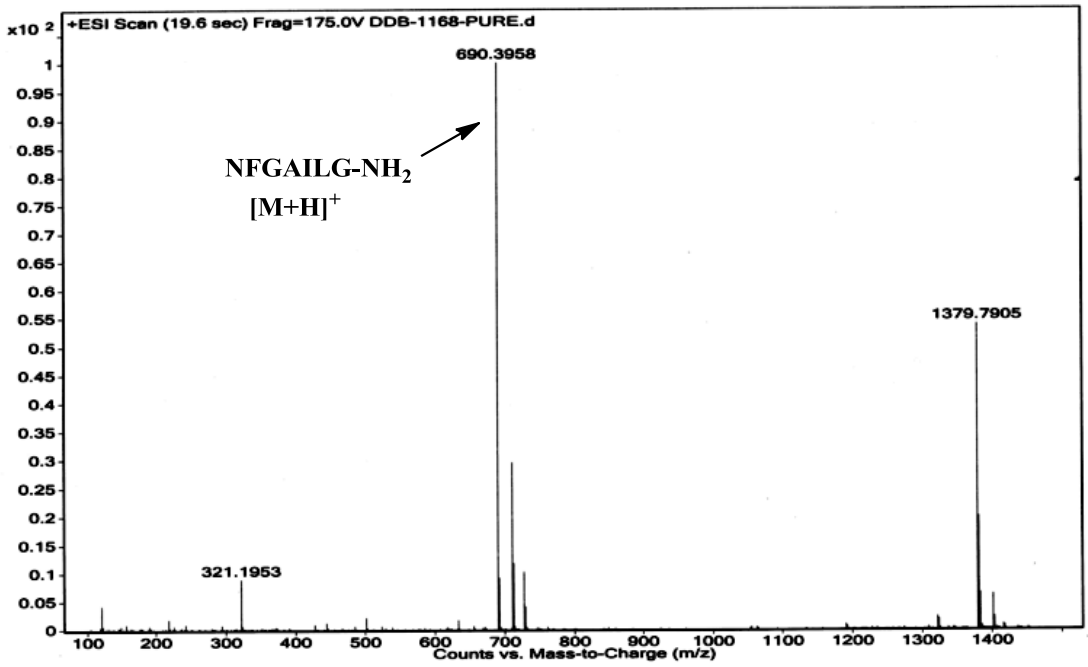


Figure S24: ESI-MS spectrum of crude NFGAILG-NH_2 peptide (Figure 2.1.2a), peak of above chromatogram.

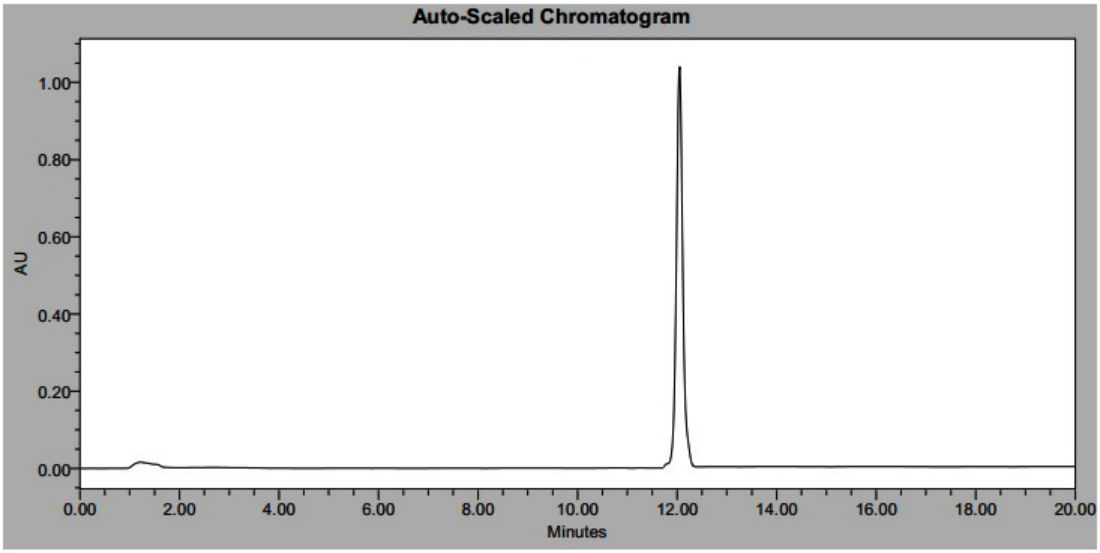


Figure S25: HPLC chromatogram of purified NFGAIILG-NH_2 (Figure 2.1.2a).

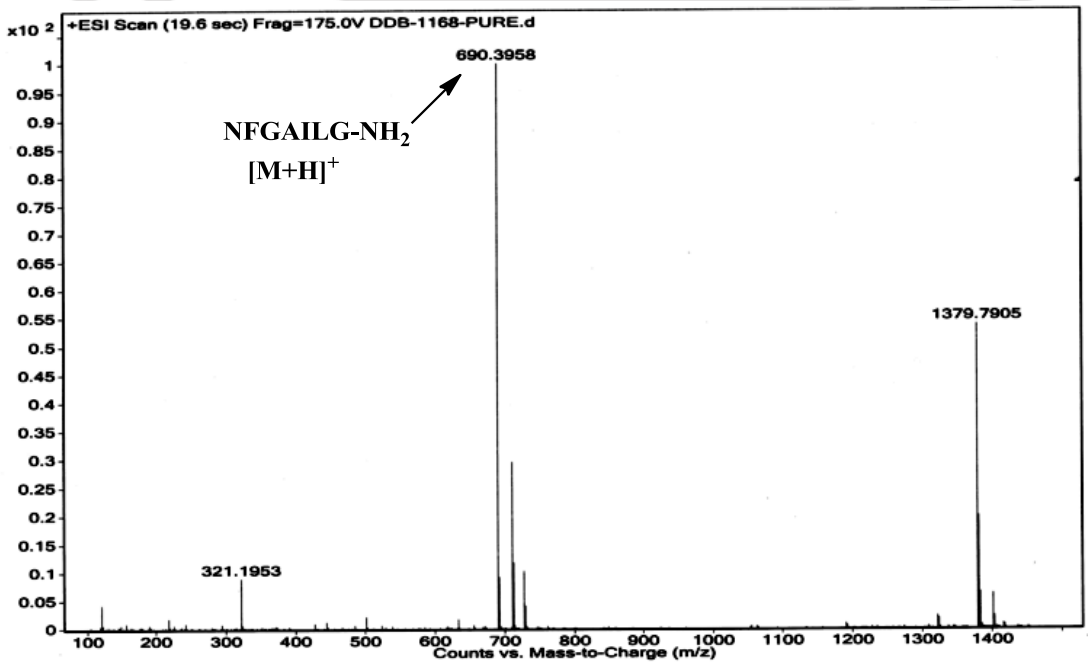


Figure S26: ESI-MS spectrum of purified NFGAILG-NH_2 peptide (Figure 2.1.2a), peak of the above chromatogram.

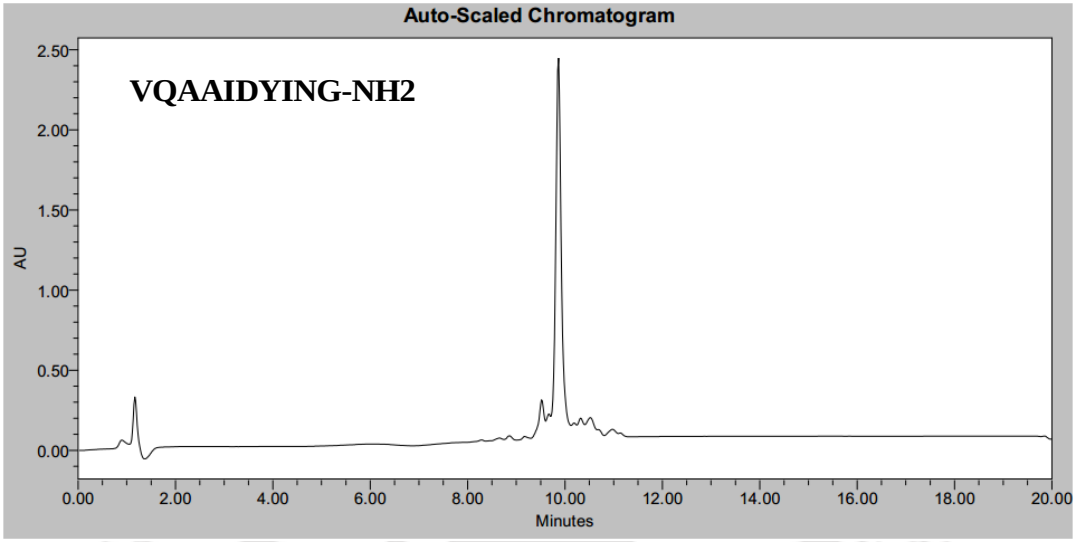


Figure S27: HPLC chromatogram of crude VQAAIDYING-NH_2 (Figure 2.1.2b).

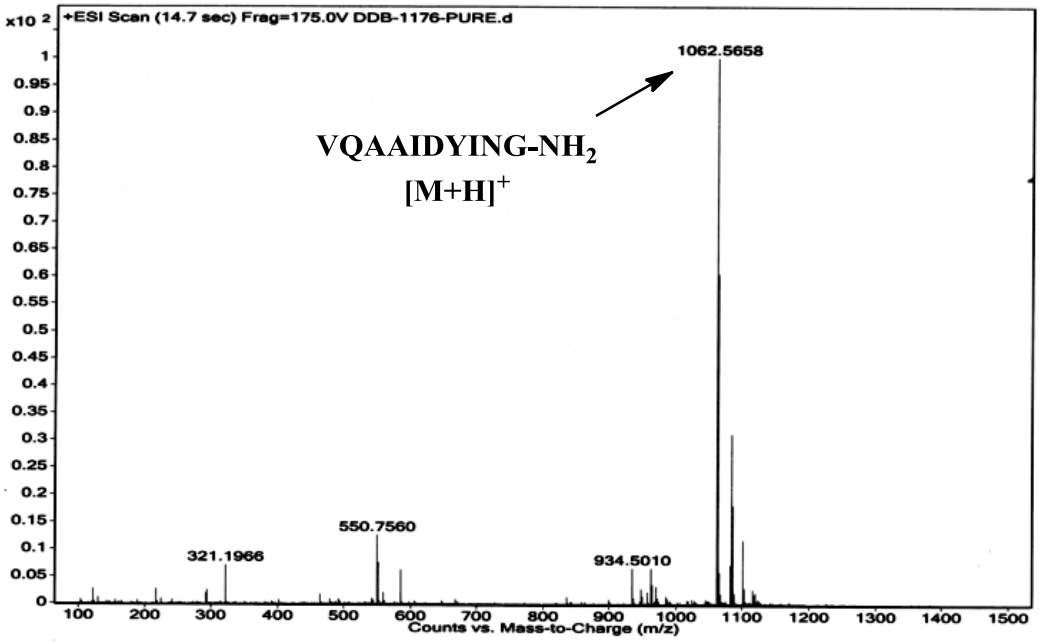


Figure S28: ESI-MS spectrum of crude VQAAIDYING-NH_2 (Figure 2.1.2b).

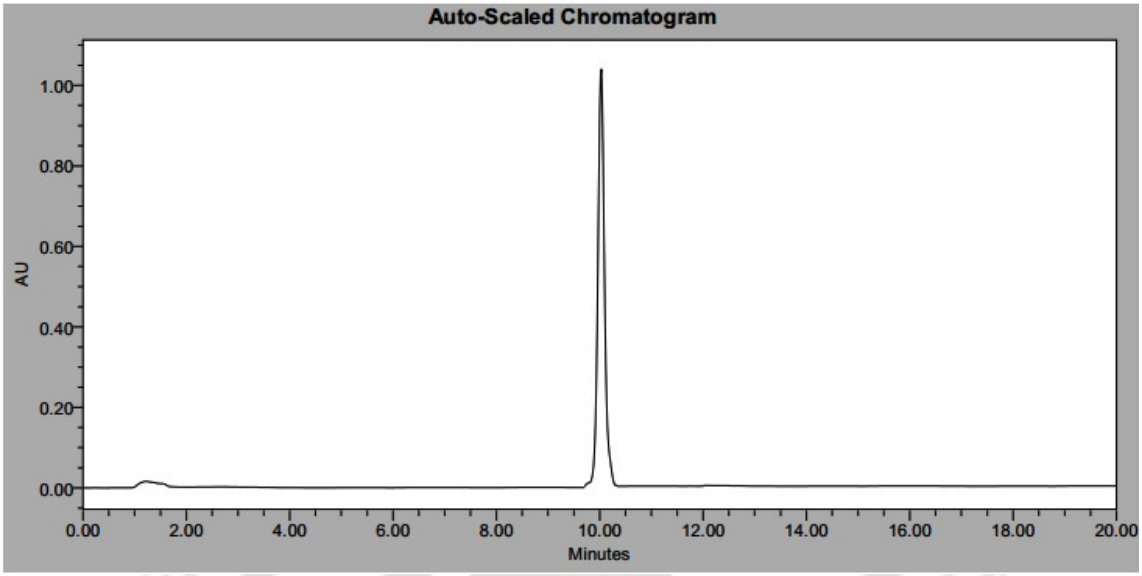


Figure S29: HPLC chromatogram of purified VQAAIDYING-NH_2 (Figure 2.1.2b).

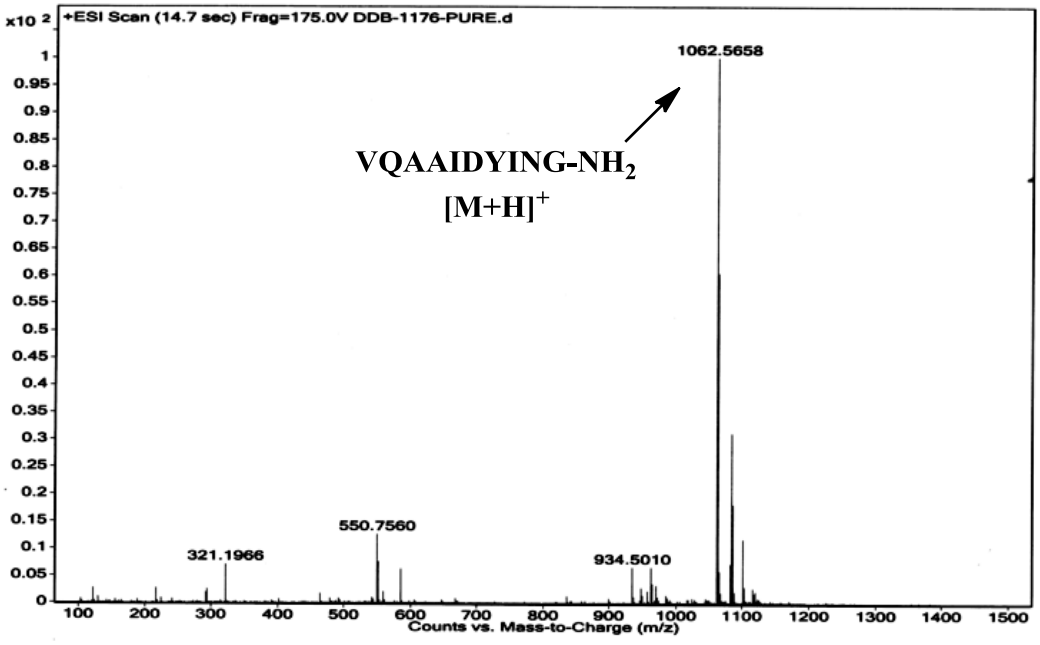
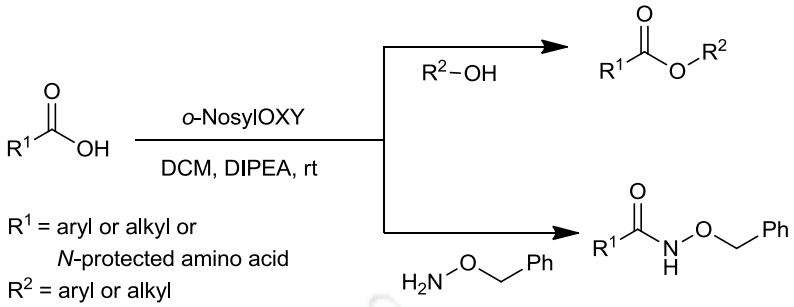


Figure S30: ESI-MS spectrum of purified VQAAIDYING-NH_2 (Figure 2.1.2b).

Chapter 3: Ethyl 2‑Cyano-2-(2-nitrobenzenesulfonyloxyimino)acetate (*o*-NosylOXY): A New Coupling Reagent for Racemization free Synthesis of Ester and Hydroxamate from Carboxylic Acids

In the previous chapter, we described the introduction of a new coupling reagent, *o*-NosylOXY and its application for the racemization free synthesis of amides and peptides. In this chapter, we showed the application of *o*-NosylOXY for the synthesis of esters and hydroxamates. Esters are found in several natural products and scaffold for various pharmaceutical compounds (Chapter 1, section 1.3.2). Hydroxamates are also important class of molecules which mostly found in siderophores as binding sites for metal encapsulation (Chapter 1, section 1.3.2). There are several methods in literature for the synthesis of esters as well as hydroxamates, although those methods suffer from some drawbacks (for esterification, chapter 1, section 1.4 and for hydroxamates, chapter 1, section 1.5). Therefore, we developed a method for the synthesis of ester and hydroxamate at room temperature using *o*-NosylOXY.

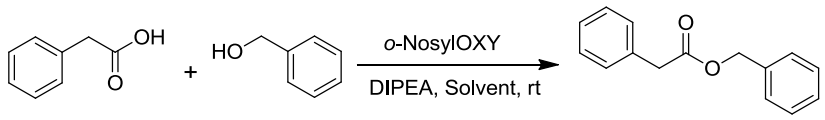


Scheme 3.1. Synthesis of ester and hydroxamate

3.1. Synthesis of esters using *o*-NosylOXY (I)

The reaction condition was optimized (*Table 3.1.1*) for esterification and hydroxamate synthesis using *o*-NosylOXY. For that we took phenylacetic acid (1 equiv) and *o*-NosylOXY (1 equiv) in different solvents as shown in table 3.1.1, then DIPEA (1.1 equiv) was added to the reaction mixture at room temperature (25 °C) with stirring. After 3-5 min preactivation, benzyl alcohol (1 equiv) and DIPEA (1.1 equiv) were added. The reaction was found to be completed in 2 h, monitored by TLC. Among the various solvents studied, DCM was observed to be the best with excellent yield (92%) of the desired product.

Table 3.1.1. Optimization of reaction[a]

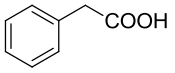
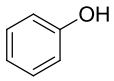
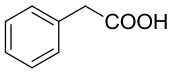
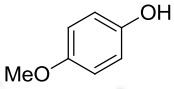
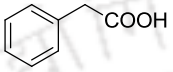
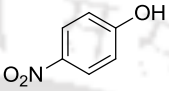
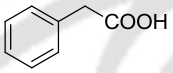
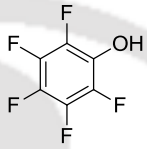
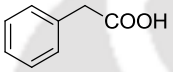
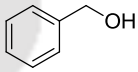
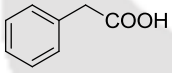
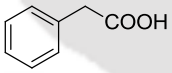
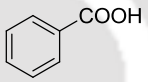
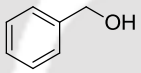
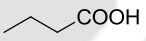
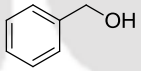
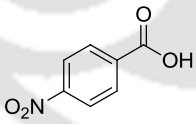
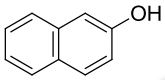
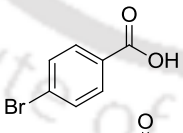
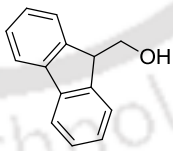
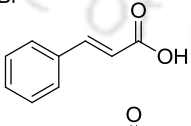
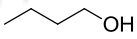
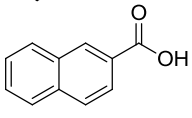
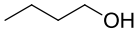


Entry	Solvent	Yield (%)[b]	Time (h)
1	Acetonitrile	71	8
2	DMSO	55	11
3	DMF	78	4
4	DCM	92	2
5	THF	51	12
6	Ethyl acetate	72	6
7	Chloroform	70	4

[a]*Performed with phenylacetic acid (1 equiv), o-NosylOXY (1 equiv), DIPEA (2.2 equiv), benzyl alcohol (1 equiv), room temperature.* [b]*Yields refer to the isolated yield after column chromatography.*

Under the above optimized condition, we investigated the substrate scope of the present protocol with various aromatic, aliphatic alcohol and carboxylic acids. The reaction of phenylacetic acid with varieties of aromatic (*entry 1-4, Table 3.1.2*) and aliphatic (*entry 5-7*) alcohols worked well. From the observation of the yields of entries 1-4, table 3.1.2, it was evident that the presence of electron donating group on phenol retards the reaction and thereby yields lesser product than its counterparts, which was in agreement with the stability of the phenoxide ions. The reaction went well with secondary (*entry 7*) and tertiary alcohol (*entry 6*).

Table 3.1.2. Scope of esterification using reagent **I**[a]

Entry	Carboxyic Acid	Alcohol	Yield(%)[b]
1			87
2			82
3			90
4			81
5			92
6			84
7			89
8			85
9			91
10			90
11			89
12			91
13			87

[a]*Performed with carboxylic acid (1 equiv), reagent* ***I*** *(1 equiv), DIPEA (2.2 equiv), alcohol (1 equiv), room temperature, 2-4 h.* [b]*Yields refer to the isolated yields after column chromatography.*

The present protocol was also successfully applied for the synthesis of biologically active esters (*entry 1, 3, 6 and 9, Table 3.1.3*).[111-114] The aliphatic carboxylic acids (*entry 1-3, Table 3.1.3*) worked well. The mentioned electromeric effect holds true for these reactions as well. In case of salicylic acid, *i.e.* entry 4, the reaction was chemoselctive and produced *p*-nitrobenzyl ester of salicylic acid as a major product; although two nucleophilic attacks were logically possible. Self-condensation was very less due to the lesser nuclephilicity of the hydroxyl group of the salicylic acid than that of the *p*-nitrobenzyl alcohol. Phenolic acids have been esterified with excellent chemoselectivity in presence of strong protic acids (Fischer esterification), but harsh reaction conditions and excess of alcohol was required to drive the reaction to a satisfactory degree of conversion,[115] whereas, it worked smoothly in the present protocol, which is milder. Furthermore, in case of entry 5 and 6 (*Table 3.1.3*) the products observed were the ester alone, not the corresponding amide. Various aliphatic primary alcohols (*entries 4-11*) and a secondary alcohol (*entry 7*) were subjected to the reaction conditions with good yields (82-90%).

Table 3.1.3. Synthesis of various carboxylic esters using **I**[a].

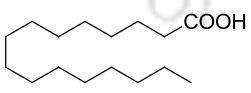
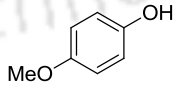
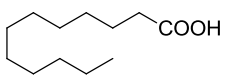
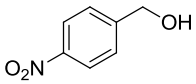
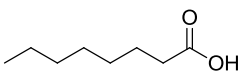
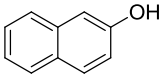
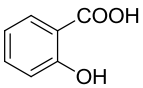
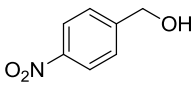
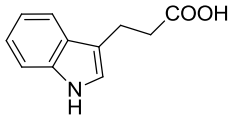
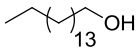
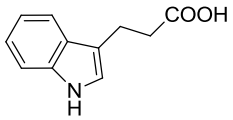
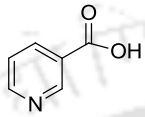
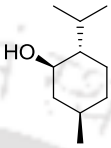
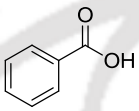
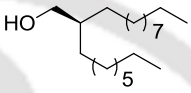
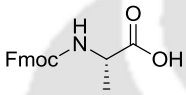
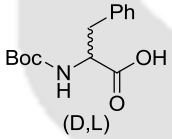
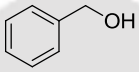
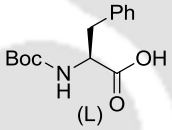
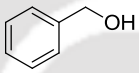
Entry	Carboxylic acid	Alcohol	Yield (%)[b]
1			86
2			92
3			91
4			82

Table 3.1.3 continued…

5			86
6			90
7			90
8			89
9		CH_3OH	87
10			90
11			89

[a]*Performed with carboxylic acid (1 equiv), reagent I (1 equiv), DIPEA (2.2 equiv), alcohol (1 equiv), room temperature, for 2-4 h.* [b]*Yields refer to the isolated yields after column chromatography.*

3.2. Racemization study

Even amino acids (*entry 9-11*, *Table 3.1.3*) retained the same reactivity towards this reaction. In order to estimate the extent of racemization, we initially synthesized Boc-DL-Phe-OBn using the mentioned protocol and the product was passed through a chiral column. Two distinct peaks, corresponding to the two enantiomers, were observed in HPLC chromatogram (*Figure 3.2.1*, Left panel). Next, we synthesized Boc-L-Phe-OBn following the same strategy. Chromatographic signature of Boc-L-Phe-OBn revealed only

one peak corresponding to the enantiopure product (*Figure 3.2.1*, Right panel). Therefore, it was inferred that the present protocol does not cause any detectable racemization.

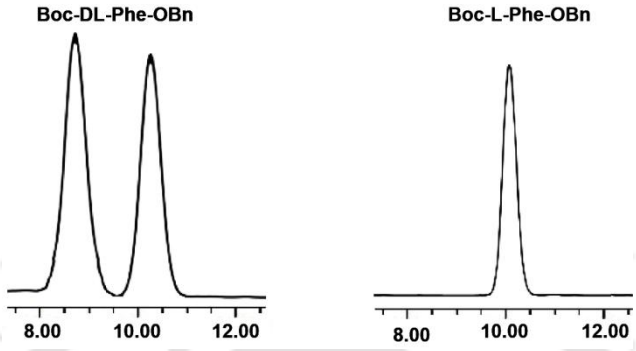
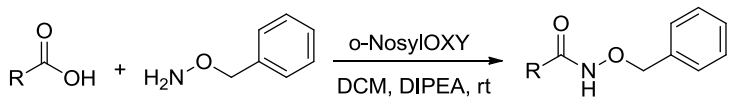


Figure 3.2.1. HPLC chromatogram of Boc-DL-Phe-OBn (Left panel) and Boc-L-Phe-OBn (Right panel, CHIRAL PAK^{R} AS-H column, 5 µm, 2.1×150 mm, an isocratic gradient of 10% isopropanol in hexane was used).

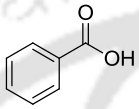
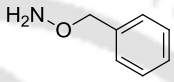
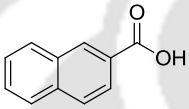
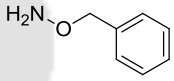
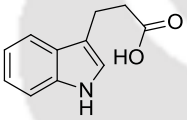
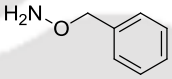
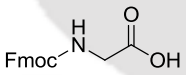
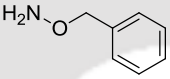
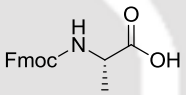
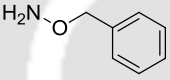
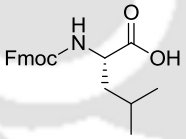
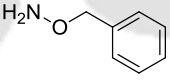
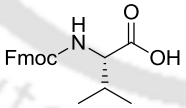
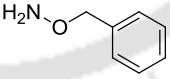
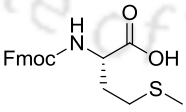
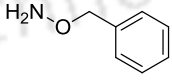
3.3. Synthesis of hydroxamates using *o*-NosylOXY

After successful synthesis of ester using *o*-NosylOXY, we further extended its scope for the synthesis of hydoxamates. Our intial trials of coupling with model substrate, *i.e.* benzoic acid with *O*-benzylhydroxylamine using reagent **I** gave the desired product with excellent yield (92%, *entry 1, Table 3.3.1*). Then it was further extended to a variety of amino acids with varying side chain complexity (*entry 4-8, Table 3.3.1).* Very good yields (81 to 92%) were obtained on stirring at room temperature (25 °C) for 2-3 h.

Table 3.3.1. Synthesis of hydroxamates using **I**[a]



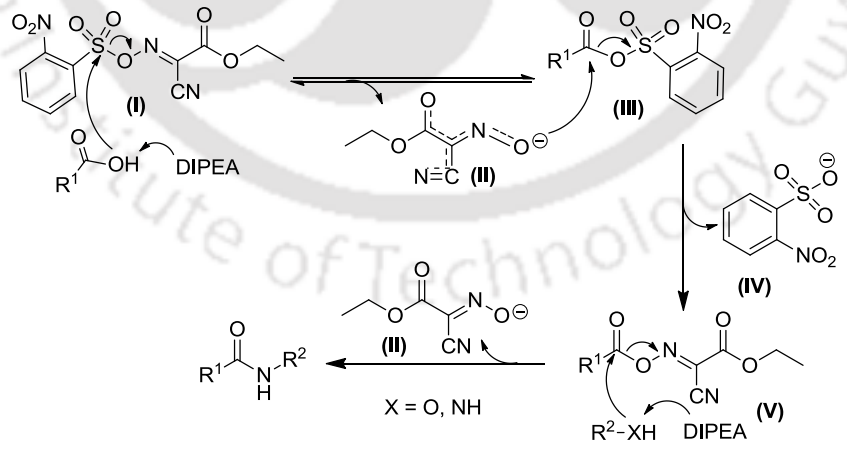
R = aryl, alkyl or Fmoc-amino acid

Entry	Carboxylic acid	O-benzylhydroxylamine	Yield (%)[b]
1			92
2			90
3			89
4			91
5			88
6			84
7			82
8			81

[a]*Performed with carboxylic acid (1 equiv), Reagent* ***I*** *(1 equiv), DIPEA (2.2 equiv), O-benzylhydroxylamine (1 equiv), room temperature, 2-3 h.* [b]*Yields were referred to the isolated yields after column chromatography.*

3.4. Plausible mechanism

A plausible mechanism was depicted in scheme 3.4.1. Initially, the nucleophile generated by the deprotonation of the carboxylic acid in presence of DIPEA, which attacked the sulfonyl centre of **I**. Expulsion of the resonance stabilized Oxyma anion **II** resulted in the mixed anhydride **III**. Further nucleophilic attack of **II** on the carbonyl carbon of **III** and expulsion of the sulfonic acid **IV** resulted in the formation of the intermediate **V**, the activated Oxyma ester of the carboxylic acid. **V** underwent nucleophilic substitution to produce the corresponding ester or hydroxamate. Isolation and complete characterization using ^{1}H NMR and ^{13}C NMR (Chapter 2, *Figure S3-S4*) and XRD analysis of the intermediate **V** was achieved (Chapter 2, *Figure 2.3.1*). The carboxylic acids are easily form activated ester with reagent **I** under mild base like DIPEA, therefore strong base is not needed for the reaction such as DBU, DABCO, *etc.* which is not good for the environment.



Scheme 3.4.1. Plausible pathways for the condensation

3.5. Conclusion

We have introduced a new and efficient coupling reagent, *o*-NosylOXY (**I**), for the synthesis of ester and hydroxamate. The present method was associated with the following important features; apparently complete retention of stereochemistry, works under ambient and milder conditions. A plausible mechanism was also depicted. The reagent can be recyclable Thus, use of this reagent reduces chemical waste generation. All these features made the reagent useful for industry and academia in the context of condensation chemistry.

3.6. Experimental Section

3.6.1. General consideration

As described in chapter 2, section 2.6.1.

3.6.2. General procedure for the synthesis of ester

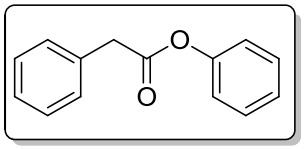
DIPEA (2.2 equiv) was added to the solution of *o*-NosylOXY (1 equiv) and carboxylic acid (1 equiv) in 2 mL of DCM. The reaction mixture was stirred for 3-5 min for preactivation followed by the addition of alcohol (1 equiv). The reaction mixture was stirred at room temperature for 2-3 h. After completion of the reaction, the reaction mixture was diluted with 50 mL of ethyl acetate; the organic phase was washed with 5% citric acid (3×20 mL), 5% $NaHCO_3$ (3×20 mL) and dried by anhydrous Na_2SO_4. Finally, Na_2SO_4 was filtered off and the solvent was evaporated to obtain the product which was purified by column chromatography.

3.6.3. General procedure for the synthesis of hydroxamate

To a solution of acid or *N*-protected amino acid (1 equiv) and *o*-NosylOXY (1 equiv) in 2 mL of DCM, DIPEA (1.1 equiv) was added. The reaction mixture was stirred for 3-5 min for preactivation followed by the addition of *O*-benzylhydroxylamine (1 equiv) and DIPEA (1.1 equiv) in 1 mL of DCM. The reaction mixture was stirred at room temperature for more 2-3 h. After completion of the reaction, the reaction mixture was diluted with 50 mL of ethyl acetate, the organic phase was washed with 5% citric acid (3×20 mL), 5% aqueous $NaHCO_3$ (3×20 mL), brine and dried over anhydrous Na_2SO_4. Finally, Na_2SO_4 was filtered and the solvent was evaporated. The product was purified by silica gel column chromatography.

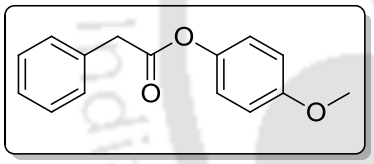
3.7. Characterization data

Phenyl 2-phenylacetate[116] (entry 1, Table 3.1.2)



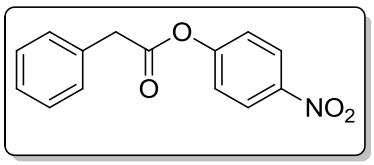
Yield: 184 mg (87%); yellowish oil; R_f = 0.51 (EtOAc:Hexane, 1.0:9.0); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.30 (m, 7H), 7.22-7.18 (m, 1H), 7.05-7.04 (m, 2H), 3.85 ppm (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 151.2, 134.0, 129.8, 129.7, 129.1, 127.7, 126.2, 121.8, 41.7 ppm; IR (KBr): 2924, 2853, 1759, 1593, 1398, 1261, 1088, 1016, 696; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_{13}O_2$ 213.091, found 213.0911.

4-Methoxyphenyl 2-phenylacetate (entry 2, Table 3.1.2)



Yield: 198 mg (82%); clear oil; R_f = 0.50 (EtOAc:Hexane, 1.0:9.0); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.35 (m, 5H), 6.97-6.95 (d, *J* = 8.0 Hz, 2H), 6.86-6.84 (d, *J* = 8.0 Hz, 2H), 3.83 (s, 2H), 3.76 ppm (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 170.9, 157.5, 144.6, 133.7, 129.5, 128.9, 127.5, 122.4, 114.6, 55.7, 41.5 ppm; IR (KBr): 2930, 2837, 1754, 1509, 1267, 1188, 1016, 544 cm^{-1}; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{15}H_{14}NaO_3$ 265.0835, found 265.0832.

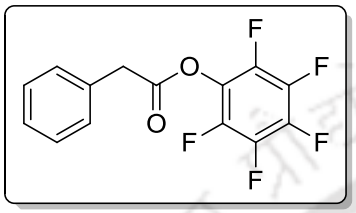
4-Nitrophenyl 2-phenylacetate (entry 3, Table 3.1.2)



Yield: 231 mg (90%); clear oil; R_f = 0.50 (EtOAc/Hexane, 1.0:9.0); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26-8.23 (d, *J* = 8.0 Hz, 2H), 7.39-7.37 (m, 5H), 7.26-7.24 (d, *J* = 8.0 Hz, 2H), 3.90 ppm (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 169.3, 155.6, 145.5, 130.5, 129.5, 128.8, 127.9, 125.5, 122.5, 41.5 ppm; IR (KBr): 2924, 2851, 1764,

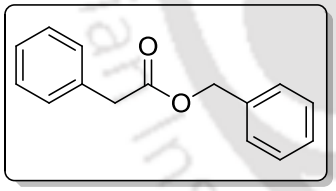
1593, 1524, 1347, 1216, 1114 cm^{-1}; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{14}H_{11}NNaO_4$ 280.0586, found 280.0583.

Pentafluorophenyl 2-phenylacetate[117] (entry 4, Table 3.1.2)



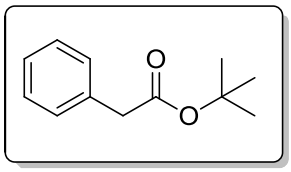
Yield: 245 mg (81%); clear oil; R_f = 0.51 (EtOAc:Hexane, 1.0:9.0); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.38 (m, 2H), 7.36-7.32 (m, 3H), 3.96 ppm (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.7, 132.3, 129.4, 129.2, 129.0, 128.8, 128.0, 127.7, 40.1 ppm; IR (KBr): 3055, 2929, 1776, 1740, 1456, 1220, 1094, 1003, 732, 696, 557 cm^{-1}; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{14}H_7F_5NaO_2$ 325.0258, found 325.0256.

Benzyl 2-phenylacetate[118] (entry 5, Table 3.1.2)



Yield: 229 mg (92%), colorless oil; R_f = 0.60 (EtOAc:Hexane, 1.0:9.0); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.31 (m, 5H), 7.28-7.26 (m, 5H), 5.13 (s, 2H), 3.67 ppm (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 171.4, 135.9, 134.0, 129.3, 128.6, 128.6, 128.2, 128.1, 127.2, 66.6, 41.3 ppm; IR (KBr): 3032, 1737, 1497, 1455, 1259, 1146, 725, 491 cm^{-1}; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{15}H_{14}NaO_2$ 249.0886, found 249.0889.

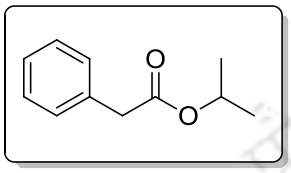
***tert*-Butyl 2-phenylacetate[119] (entry 6, Table 3.1.2)**



Yield: 161 mg (84%); clear oil; R_f = 0.50 (EtOAc:Hexane, 1.0:9.0); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.22 (m, 5H), 3.51 (s, 2H), 1.45 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9,

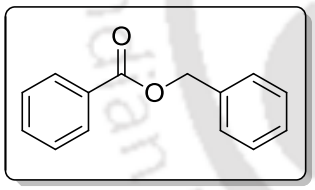
134.7, 129.2, 128.5, 126.8, 80.7, 42.6, 28.0 ppm; IR (KBr): 3230, 2989, 1754, 1243, 752, 543 cm^{-1}; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{12}H_{16}NaO_2$ 215.1048, found 215.1051.

Isopropyl 2-phenylacetate (entry 7, Table 3.1.2)



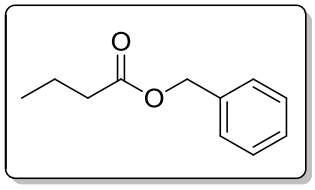
Yield: 158 mg (89%); clear oil; R_f = 0.51 (EtOAc:Hexane, 1.0:9.0); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.29 (m, 3H), 7.28-7.26 (m, 2H), 5.03-4.97 (m, 1H), 3.57 (s, 2H), 1.21 ppm (d, *J* = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.2, 134.4, 129.3, 128.6, 127.0, 68.2, 41.8, 21.8 ppm; IR (KBr): 2934, 2827, 1754, 1522, 1436, 1266, 1126, 563 cm^{-1}; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{11}H_{14}NaO_2$ 201.0891, found 201.0894.

Benzyl benzoate[116] (entry 8, Table 3.1.2)



Yield: 180 mg (85%); colorless oil; R_f = 0.50 (EtOAc:Hexane, 2.0:8.0); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09-8.06 (d, *J* = 7.2 Hz, 2H), 7.57-7.53 (t, 1H), 7.45-7.42 (m, 3H), 7.40-7.33 (m, 4H), 5.39 ppm (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.5, 136.2, 133.1, 130.3, 129.8, 128.7, 128.5, 128.4, 128.3, 66.8 ppm; IR (KBr): 2853, 1749, 1543, 1352, 1273, 1043, 654, 544 cm^{-1}; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{14}H_{12}NaO_2$ 235.0735, found 235.0738.

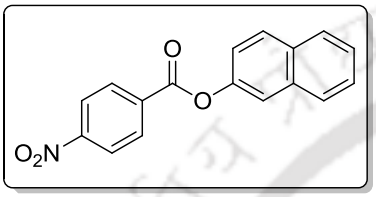
Benzyl butyrate[120] (entry 9, Table 3.1.2)



Yield: 162 mg (91%); oily; R_f = 0.50 (EtOAc:Hexane, 0.5:9.5); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.34 (m, 1H), 7.31-7.30 (m, 4H), 5.10 (s, 2H), 2.34-2.31 (t, *J* = 8.0 Hz, 2H), 1.69-1.64 (q, 2H), 0.95-0.92 ppm (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ

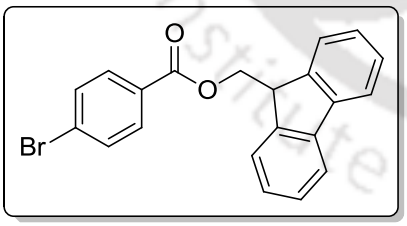
173.5, 136.3, 128.6, 128.2, 66.1, 36.2, 18.5, 13.7 ppm; IR (KBr): 2928, 1738, 1754, 1381, 1253, 1171, 697 cm^{-1}; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{11}H_{14}NaO_2$ 201.0891, found 201.0889.

Naphthalen-2-yl 4-nitrobenzoate (entry 10, Table 3.1.2)



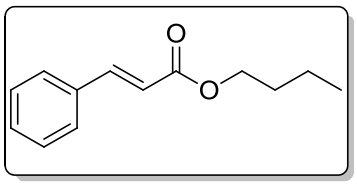
Yield: 263 mg (90%); white solid; R_f = 0.51 (EtOAc:Hexane, 1.0:9.0); m.p.167-170 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.07 (s, 1H), 8.65-8.54 (d, *J* = 8.0 Hz, 1H), 8.50-8.48 (d, *J* = 8.0 Hz, 1H), 7.92-7.84 (m, 3H), 7.75-7.70 (m, 2H), 7.52-7.49 (m, 2H) 7.37-7.34 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.6, 151.0, 148.3, 135.1, 133.9, 131.8, 131.4, 129.9, 128.0, 127.9, 127.8, 127.0, 126.8, 126.2, 126.0, 123.9, 120.8, 118.7 ppm; IR (KBr): 2922, 2852, 1724, 1593, 1424, 1347, 1299, 1096 cm^{-1}; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{17}H_{11}NNaO_4$ 316.0586, found 316.0583.

(9H-fluoren-9-yl)methyl 4-bromobenzoate[121] (entry 11, Table 3.1.2).



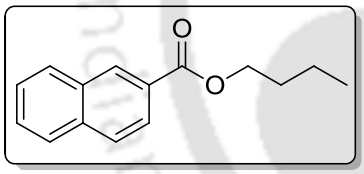
Yield: 336 mg (89%); white crystalline solid; R_f = 0.50 (EtOAc:Hexane, 1.0:9.0); m.p.98-102 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91-7.89 (d, *J* = 8.0 Hz, 2H), 7.78-7.76 (d, *J* = 8.0 Hz, 2H), 7.61-7.59 (m, 4H), 7.42-7.48 (t, *J* = 8.0 Hz, 2H), 7.32-7.28 (t, *J* = 8.0 Hz, 2H), 4.61-4.59 (d, *J* = 8.0 Hz, 2H), 4.37-4.35 ppm (t, *J* = 8.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 165.9, 143.8, 141.5, 132.1, 131.3, 129.2, 128.4, 128.0, 127.3, 125.1, 120.3, 67.4, 47.1 ppm; IR (KBr): 3030, 2890, 1727, 1590, 1452, 1241, 1118, 1010, 751, 551 cm^{-1}; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{21}H_{15}BrNaO_2$ 401.0153, found 401.0157.

Butyl cinnamate (entry 12, Table 3.1.2)



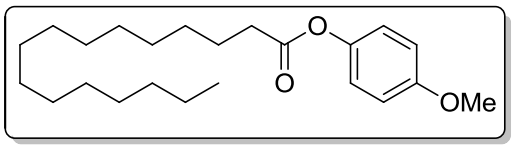
Yield: 186 mg (91%); clear oil; R_f = 0.50 (EtOAc:Hexane, 1.0:9.0); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68-7.64 (d, *J* = 12.0 Hz, 1H), 7.51-7.49 (m, 2H), 7.37-7.35 (m, 3H), 6.44-6.40 (d, *J* = 8.0 Hz, 1H), 4.20-4.17 (t, *J* = 8.0 Hz, 2H), 1.70-1.63 (m, 2H), 1.44-1.39 (m, 2H), 0.96-0.92 ppm (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 167.2, 144.6, 134.6, 130.3, 129.0, 128.1, 118.47, 64.5, 30.9, 19.3, 13.8 ppm; IR (KBr): 2960, 2873, 1714, 1638, 1450, 1311, 1172, 980, 767, 684, 486 cm^{-1}; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{13}H_{16}NaO_2$ 227.1048, found 227.1045.

Butyl 2-naphthoate (entry 13, Table 3.1.2)



Yield: 198 mg (87%); oily; R_f = 0.51 (EtOAc:Hexane, 1.0:8.0); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.60 (s, 1H), 8.08-8.06 (d, *J* = 8.0 Hz, 2H), 8.93-8.91 (d, *J* = 8.0 Hz, 2H), 7.84-7.81 (m, 2H), 4.39-4.36 (t, *J* = 4.0 Hz, 2H), 1.82-1.75 (q, 2H), 1.53-1.47 (q, 2H), 1.01-0.98 ppm (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 135.5, 132.5, 130.9, 129.3, 128.2, 127.8, 126.6, 125.3, 65.0, 30.9, 19.4, 13.8 ppm; IR (KBr): 2959, 2873, 1716, 1632, 1466, 1286, 1196, 955, 779, 474 cm^{-1}; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{15}H_{16}NaO_2$ 251.1048, found 251.1051.

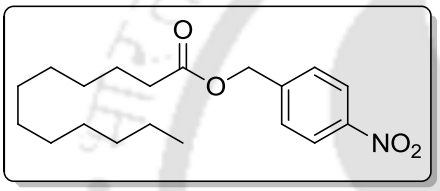
4-Methoxyphenyl palmitate[111] (entry 1, Table 3.1.3)



Yield: 311 mg (86%); white solid powder; R_f = 0.50 (EtOAc:Hexane, 0.5:9.5); m.p.52-52

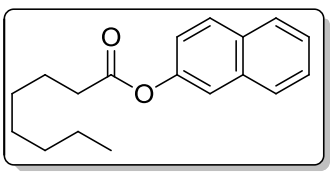
°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.98-6.95 (d, *J* = 8.0 Hz, 2H), 6.87-6.85 (d, *J* = 8.0 Hz, 2H), 3.77 (s, 3H), 2.52-2.48 (t, *J* = 8.0 Hz, 2H), 1.72-1.70 (m, 2H), 1.26-1.21 (m, 24H), 0.87-0.84 ppm (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.8, 157.3, 144.5, 122.4, 114.5, 55.6, 34.5, 32.1, 29.8, 29.7, 29.6, 29.5, 29.4, 29.2, 25.1, 22.9 14.3 ppm; IR (KBr): 2916, 2849, 1746, 1552, 1509, 1463, 1213, 1033, 844 cm^{-1}; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{23}H_{38}NaO_3$ 385.2719, found 385.2716.

4-Nitrobenzyl tetradecanoate (entry 2, Table 3.1.3)



Yield: 308 mg (92%); oily R_f = 0.51 (EtOAc:Hexane, 0.5:9.5); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20-8.18 (d, *J* = 8.0 Hz, 2H), 7.49-7.47 (d, *J* = 8.0 Hz, 2H), 5.17 (s, 2H), 2.38 (t, *J* = 8.0 Hz, 2H), 1.64-1.60 (m, 2H), 1.26-1.21 (m, 16H), 0.85-0.82 ppm (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.4, 147.7, 143.6, 128.4, 123.8, 64.6, 34.3, 32.0, 29.7, 29.5, 29.4, 29.3, 29.2, 25.0, 22.8, 14.2 ppm; IR (KBr): 2926, 2853, 1743, 1607, 1524, 1347, 1015, 859, 738 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{19}H_{30}NO_4$ 336.2175 found 336.2171.

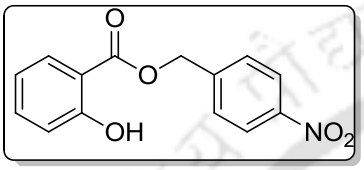
Naphthalen-2-yl octanoate [112] (entry 3, Table 3.1.3)



Yield: 246 mg (91%); white solid; R_f = 0.50 (EtOAc:Hexane, 1.0:9.0); m.p.42-43 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83-7.81 (m, 2H), 7.78-7.76 (d, *J* = 8.0 Hz, 1H), 7.53 (s, 1H), 7.46-7.43 (m, 2H), 7.22-7.19 (m, 1H), 2.61-2.57 (t, *J* = 8.0 Hz, 2H), 1.81-1.74 (m, 2H), 1.43-1.31 (m, 8H), 0.91-0.88 ppm (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 172.6, 148.6, 134.0, 131.6, 129.5, 127.9, 127.8, 126.7, 125.8,

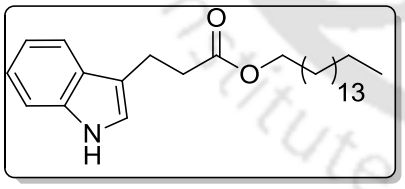
121.4, 118.7, 34.6, 31.8, 29.3, 29.1, 25.2, 22.8, 14.2 ppm; IR (KBr): 2928, 2852, 1751, 1510, 1211, 1162, 812, 634, 483 cm^{-1}; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{18}H_{22}NaO_2$ 293.1517, found 293.1521.

4-Nitrophenyl 2-hydroxybenzoate[122] (entry 4, Table 3.1.3)



Yield: 224 mg (82%); colourless solid; R_f = 0.50 (EtOAc:Hexane, 1.0:9.0); ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.53 (s, 1H), 8.25-8.23 (d, *J* = 8.0 Hz, 2H) 7.88-7.86 (d, *J* = 8.0 Hz, 1H), 7.60-7.58 (d, *J* = 8.0 Hz, 2H), 7.49-7.45 (t, *J* = 8.0 Hz, 1H), 6.99-6.97 (d, *J* = 8.0 Hz, 1H), 6.91-6.87 (t *J* = 8.0 Hz, 1H), 5.22 ppm (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7, 162.0, 148.0, 142.6, 136.4, 129.9, 128.6, 124.0, 119.5, 117.9, 112.0, 65.5 ppm; IR (KBr): 3427, 2967, 2851, 1725, 1524, 1339, 1253, 754, 532 cm^{-1}; HRMS (ESI): m/z $[M-H]^-$ calcd for $C_{14}H_{10}NO_5$ 272.0559, found 272.0557.

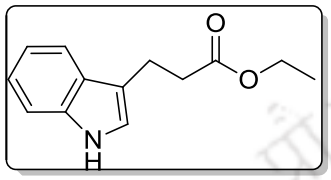
Hexadecyl 3-(1H-indol-3-yl)propanoate[123] (entry 5, Table 3.1.3)



Yield: 355 mg (86%); yellowish crystalline solid; R_f = 0.50 (EtOAc:Hexane, 2.0:8.0); m.p. 60-62 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (br, 1H), 7.60-7.58 (d, *J* = 8.0 Hz, 1H), 7.34-7.32 (d, *J* = 8.0 Hz, 1H), 7.20-7.16 (t, *J* = 8.0 Hz, 1H), 7.13-7.09 (t, *J* = 8.0 Hz, H), 6.98 (s, 1H), 4.07-4.04 (t, 2H), 3.11-3.07 (t, *J* = 8.0 Hz, 2H), 2.72-2.68 (t, *J* = 8.0 Hz, 2H), 1.59-1.57 (m, 2H), 1.26-1.23 (m, 26H), 0.90-0.85 ppm (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.8, 136.5, 127.3, 122.1, 121.6, 119.4, 118.8, 115.0, 111.3, 64.8, 35.2, 32.1, 29.8, 29.7, 29.5, 29.4, 28.8, 26.1, 25.8, 22.8, 20.8, 14.3 ppm; IR

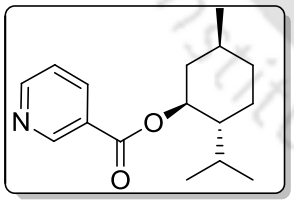
(KBr): 3342, 2916, 2848, 1718, 1471, 1279, 1186, 734, 552 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{27}H_{44}NO_2$ 414.3372, found 414.3368.

Ethyl 3-(indolin-3-yl)propanoate[113b] (entry 6, Table 3.1.3)



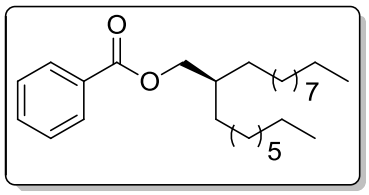
Yield: 195 mg (90%); yellowish solid; R_f = 0.50 (EtOAc:Hexane, 2.0:8.0); m.p. 39-41 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (br, 1H), 7.60-7.58 (d, *J* = 8.0 Hz, 1H), 7.30-7.28 (d, *J* = 8.0 Hz, 1H), 7.19-7.15 (t, *J* = 8.0 Hz, 1H), 7.12-7.08 (t, *J* = 8.0 Hz, H), 6.97 (s, 1H), 4.15-4.07 (q, 2H), 3.11-3.07 (t, *J* = 8Hz, 2H), 2.72-2.68 (t, *J* = 8.0 Hz, 2H), 1.23-1.19 ppm (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.8, 136.4, 127.2, 122.0, 121.7, 119.2, 118.7, 114.6, 111.3, 60.5, 35.1, 20.7, 14.2 ppm; IR (KBr): 3345, 2926, 2841, 1728, 1472, 1272, 1183, 724, 562 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{13}H_{16}NO_2$ 218.1181, found 218.1177.

(1S, 2R, 5S)-2-isopropyl-5-methylcyclohexyl nicotinate[123] (entry 7, Table 3.1.3)



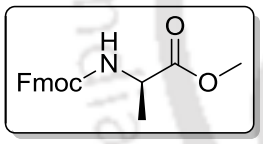
Yield: 235 mg (90%); oily R_f = 0.50 (EtOAc:Hexane, 1.0:9.0); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.18 (s, 1H, 1×ArH), 8.73-8.71 (d, *J* = 8.0 Hz, 1H), 8.26-8.24 (d, *J* = 8.0 Hz, 1H), 7.36-7.33 (t, *J* = 8.0 Hz, 1H), 4.96-4.89 (s, 1H), 2.10-2.05 (m, 1H), 1.91-1.87 (m, 1H), 1.72-1.67 (m, 2H), 1.56-1.49 (m, 2H), 1.12-1.06 (m, 2H), 0.93-0.88 (m, 6H), 0.76-074 ppm (d, *J* = 8.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 164.9, 153.3, 151.0, 137.2, 126.8, 123.4, 75.7, 47.3, 41.0, 34.4, 31.6, 26.7, 23.8, 22.1, 20.9, 16.6 ppm; IR (KBr): 2957, 2870, 1719, 1591, 1289, 1121, 741 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{16}H_{24}NO_2$ 262.1807, found 262.1810.

2-Octyldodecyl benzoate (entry 8, Table 3.1.3)



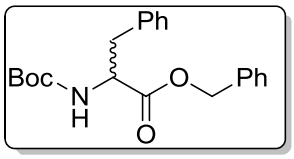
Yield: 358 mg (89%); oily R_f = 0.50 (EtOAc:Hexane, 0.5:9.5); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03-8.01 (d, *J* = 8.0 Hz, 2H), 7.55-7.53 (m, 1H), 7.42-7.40 (m, 2H), 4.21-4.17 (m, 1H), 1.76-1.74 (m, 1H), 1.29-1.23 (m, 32H), 0.86-0.83 ppm (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 166.8, 132.8, 130.7, 129.8, 129.4, 128.4, 128.1, 67.8, 37.6, 37.3, 32.1, 31.8, 31.6, 31.3, 31.1, 30.1, 29.8, 29.7, 29.5, 27.0, 26.8, 26.6, 22.8, 22.6, 14.3, 14.0 ppm; IR (KBr): 2925, 2854, 1723, 1466, 1272, 1133, 710 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{27}H_{46}NaO_2$ 425.3319, found 425.3314.

Methyl 2-(((9H-fluoren-9-yl)methoxy)carbonyl) propanoate[114b] (entry 9, Table 3.1.3)



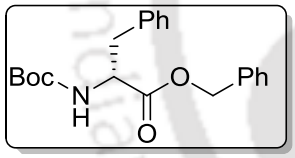
Yield: 283 mg (87%); white solid; R_f = 0.51 (EtOAc:Hexane, 2.0:8.0); m.p.106-108 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75-7.73 (d, *J* = 8.0 Hz, 2H), 7.59-7.57 (m, 2H), 7.40-7.36 (t, *J* = 8.0 Hz, 2H), 7.31-7.28 (t, *J* = 8.0 Hz, 2H), 5.34 (br, 1H), 4.39-4.36 (m, 3H), 4.22-4.19 (t, *J* = 8.0 Hz, 1H), 3.74 (s, 3H), 1.42-1.41 ppm (d, *J* = 4.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.7, 155.8, 144.0, 141.4, 127.8, 127.2, 125.2, 120.1, 67.1, 52.6, 49.7, 47.2, 18.7 ppm; IR (KBr): 3330, 2924, 1747, 1690, 1536, 1267, 1084, 740 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{19}H_{19}NO_4$ 326.1392, found 326.1388.

(DL) Benzyl 2-(tert-butoxycarbonyl)-3-phenylpropanoate[124] (entry 10, Table 3.1.3)



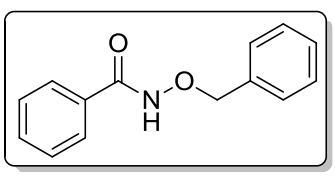
Yield: 319 mg (90%); yellowish solid; R_f = 0.50 (EtOAc:Hexane, 2.0:8.0); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.34-7.31 (m, 3H), 7.28-7.26 (d, *J* = 8.0 Hz, 2H), 7.24-7.21 (m, 3H), 7.05-7.01 (m, 2H), 5.16 (s, 2H), 5.05 (br, 1H), 4.54-4.59 (t, *J* = 4.0 Hz, 1H), 3.10-3.07 (d, *J* = 8.0 Hz, 2H), 1.42 ppm (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 171.9, 155.2, 136.1, 135.4, 129.5, 128.7, 127.1, 80.0, 67.3, 54.6, 38.4, 28.4 ppm; IR (KBr): 3456, 2923, 1732, 1688, 1521, 1223, 1087, 740 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{21}H_{26}NO_4$ 356.1862, found 356.1857.

(L) Benzyl 2-(tert-butoxycarbonyl)-3-phenylpropanoate[124] (entry 11, Table 3.1.3)



Yield: 316 mg (89%); yellowish solid; R_f = 0.51 (EtOAc:Hexane, 2.0:8.0); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.36-7.33 (m, 3H), 7.29-7.27 (d, *J* = 8.0 Hz, 2H), 7.23-7.21 (m, 3H), 7.04-7.02 (m, 2H), 5.14 (s, 2H), 5.01 (br, 1H), 4.63-4.61 (t, *J* = 4.0 Hz, 1H), 3.11-3.09 (d, *J* = 8.0 Hz, 2H), 1.41 ppm (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 171.8, 155.19, 135.9, 135.5, 129.5, 128.7, 127.1, 80.1, 67.29, 54.6, 38.4, 28.4 ppm; IR (KBr): 3456, 2923, 1732, 1688, 1521, 1223, 1087, 740 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{21}H_{26}NO_4$ 356.1862, found 356.1857.

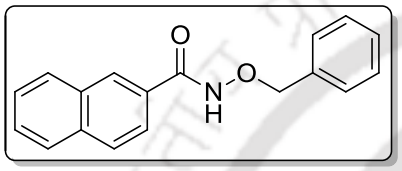
***N*-(Benzyloxy)benzamide[70] (entry 1, Table 3.3.1).**



Yield: 208 mg (92%), yellowish solid; R_f = 0.50 (EtOAc:Hexane, 2.0:8.0); m.p.107-110 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12-8.10 (m, 2H), 7.69-7.51 (m, 2H),

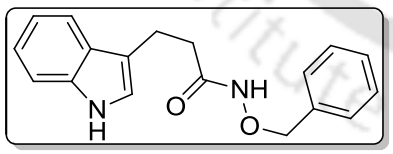
7.49-7.35 (m, 6H), 5.02 ppm (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.76, 133.75, 132.14, 130.27, 129.67, 129.43, 128.83, 128.70, 128.67, 128.55, 127.34, 78.46 ppm; IR (KBr): 2963, 1626, 1522, 1145, 1001, 747, 638 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_{14}NO_2$ 228.1025, found 228.1023.

_N_-(Benzyloxy)-2-naphthamide (entry 2, Table 3.3.1)



Yield: 249 mg (90%); white solid; R_f = 0.50 (EtOAc:Hexane, 2.0:8.0); m.p 126-129 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.01 (s, br), 8.16 (s, 1H), 7.82-7.79 (d, *J* = 8.0 Hz, 2H), 7.70-7.68 (m, 1H), 7.53-7.46 (m, 2H), 7.43-7.42 (m, 3H), 7.38-7.34 (m, 3H), 5.04 ppm (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7, 135.2, 135.0, 132.8, 129.6, 129.3, 129.1, 128.9, 128.2, 128.0, 127.1, 123.56, 78.4 ppm; IR (KBr): 3208, 2920, 1647, 1501, 1123, 908, 752, 699, 533, 505 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{18}H_{16}NO_2$ 278.1181, found 278.1185.

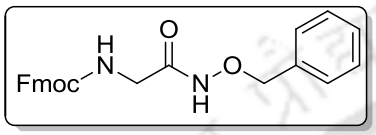
_N_-(Benzyloxy)-3-(1*H*-indol-3-yl)propanamide[125] (entry 3, Table 3.3.1)



Yield: 261 mg (89%), white solid; R_f = 0.50 (EtOAc:Hexane, 2.0:8.0); m.p. 145-147 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57-7.55 (d, *J* = 8.0 Hz, 1H), 7.37-7.35 (d, *J* = 8.0 Hz, 1H), 7.27-7.34 (m, 3H), 7.18-7.16 (m, 3H), 7.09-7.05 (m, 1H), 6.98 (s, 1H), 4.70 (s, 2H), 3.10-3.06 (t, *J* = 8.0 Hz, 2H), 2.42-2.38 ppm (t, *J* = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.02, 136.36, 135.06, 129.00, 128.28, 128.11, 128.11, 126.84, 122.01, 121.26, 118.50, 118.13, 113.28, 111.15, 76.91, 33.67, 20.95 ppm;

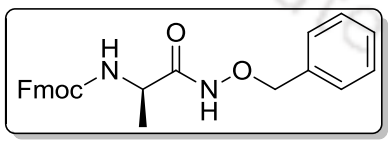
IR (KBr): 3402, 2922, 1656, 1502, 1145, 1001, 743, 698, 616, 516 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{18}H_{19}N_2O_2$ 295.1447, found 295.1443.

(9*H*-Fluoren-9-yl)methyl 2-(benzyloxyamino)-2-oxoethyl carbamate (entry 4, Table 3.3.1)



Yield: 366 mg (91%); white solid; R_f = 0.40 (EtOAc:Hexane, 4.0:6.0); m.p 114-118 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.34 (br, 1H), 7.76-7.73 (d, *J* = 8.0 Hz, 2H), 7.41-7.38 (m, 2H), 7.36-7.27 (m, 4H), 7.15-7.11 (m, 5H), 5.58 (br, 1H), 4.85 (s, 2H), 4.26-4.24 (d, *J* = 8.0 Hz, 2H), 4.07-4.06 (d, *J* = 4.0 Hz, 2H), 3.69 ppm (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.1, 156.9, 143.8, 141.4, 129.4, 128.9, 128.7, 127.9, 127.2, 125.2, 120.1, 78.5, 67.5, 47.2, 42.6 ppm; IR (KBr): 3334, 2912, 1702, 1674, 1540, 1272, 1167, 756, 698, 534 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{24}H_{23}N_2O_4$ 403.1658, found 403.1654.

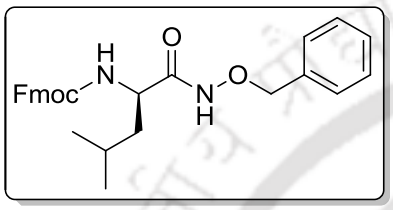
(9*H*-Fluoren-9-yl)methyl 1-(benzyloxyamino)-1-oxopropan-2-ylcarbamate[69] (entry 5, Table 3.3.1)



Yield: 366 mg (88%); white solid; R_f = 0.50 (EtOAc:Hexane, 4.0:6.0); m.p 142-144 °C; $[\alpha]_D^{25}$ = -13.4 ($CHCl_3$, c = 0.10); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.27 (br, 1H), 7.75-7.73 (d, *J* = 8.0 Hz, 2H), 7.54-7.53 (d, *J* = 4.0 Hz, 2H), 7.38-7.32 (m, 4H), 7.31-7.25 (m, 5H), 5.51 (br, 1H), 4.86 (s, 2H), 4.30 (d, *J* = 4.0 Hz, 2H), 4.14-4.12 (m, 2H), 1.25 ppm (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 169.9, 156.2, 143.7, 141.4, 135.1, 129.3, 128.9, 128.7, 127.9, 127.2, 125.2, 120.1, 78.3, 67.3, 48.2, 47.1, 18.0 ppm;

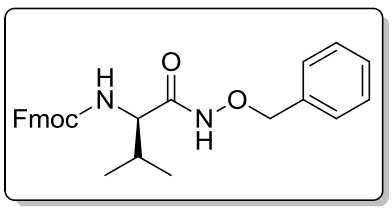
IR (KBr): 3294, 2923, 1690, 1664, 1537, 1260, 755, 739, 521 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{25}H_{25}N_2O_4$ 417.1814, found 417.1811.

(9*H*-Fluoren-9-yl)methyl 1-(benzyloxyamino)-4-methyl-1-oxopentan-2-ylcarbamate (entry 6, Table 3.3.1)



Yield: 385 mg (84%); white solid; R_f = 0.50 (EtOAc:Hexane, 3.0:7.0); m.p 157-160 °C; $[\alpha]_D^{25}$ = -12.4 ($CHCl_3$, c = 0.41); ^1H NMR (400 MHz, $CDCl_3$): δ 9.59 (br, 1H), 7.73-7.71 (d, *J* = 8.0 Hz, 2H), 7.57-7.49 (m, 4H), 7.35-7.25 (m, 7H), 5.59 (d, *J* = 8.0 Hz, 1H), 4.85 (s, 2H), 4.29-4.27 (d, *J* = 8.0 Hz, 2H), 4.23-4.20 (t, *J* = 8.0 Hz, 1H), 4.14-4.12 (t, *J*= 8.0 Hz, 1H), 1.57-1.54 (m, 2H), 0.92-0.91 ppm (d, *J* = 4.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 156.4, 143.7, 141.3, 135.1, 129.3, 128.7, 128.5, 127.4, 127.1, 125.1, 120.0, 78.2, 67.3, 50.9, 47.0, 41.3, 24.7, 22.6, 22.4 ppm; IR (KBr): 3311, 2957, 1688, 1666, 1535, 1248, 1040, 765, 532, 458 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{28}H_{31}N_2O_4$ 459.2284, found 459.2279.

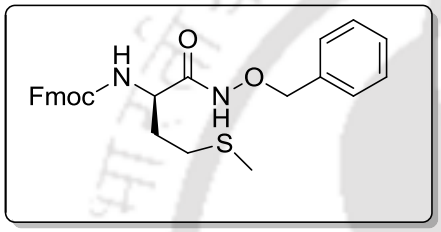
(9*H*-Fluoren-9-yl)methyl 1-(benzyloxyamino)-3-methyl-1-oxobutan-2-ylcarbamate (entry 7, Table 3.3.1)



Yield: 364 mg (82%); white solid; R_f = 0.40 (EtOAc:Hexane, 3.0:7.0); m.p 205-208 °C; $[\alpha]_D^{25}$ = -18.7 ($CHCl_3$, c = 0.50); ^1H NMR (400 MHz, $CDCl_3$): δ 9.54 (br, 1H), 7.73-7.71 (d, *J* = 8.0 Hz, 2H), 7.53-7.51 (m, 2H), 7.36-7.35 (m, 3H), 7.27-7.24 (m, 6H), 5.72-5.70 (d, *J* = 8.0 Hz, 1H), 4.84 (s, 2H), 4.30-4.28 (d, *J* = 8.0 Hz, 2H), 4.22-4.19 (d, *J* = 4.0 Hz, 1H), 2.04-2.01 (m, 1H), 0.91

ppm (d, *J* = 4.0 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 169.0, 156.7, 143.8, 141.4, 135.1, 129.4, 128.9, 128.6, 127.3, 127.2, 125.3, 120.1, 78.5, 67.4, 58.3, 47.2, 31.1, 19.2, 18.5 ppm; IR (KBr): 3281, 2961, 1698, 1657, 1544, 1294, 1251, 748, 742, 541 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{27}H_{29}N_2O_4$ 445.2127, found 445.2131.

(9*H*-Fluoren-9-yl)methyl 1-(benzyloxyamino)-4-(methylthio)-1-oxobutan-2-yl-carbamate (entry 8, Table 3.3.1)



Yield: 385 mg (81%); white solid; R_f = 0.50 (EtOAc:Hexane, 3.0:7.0); m.p 171-174 °C; $[\alpha]_D^{25}$ = -15.3 ($CHCl_3$, c = 0.37); ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.05 (br, 1H), 7.76-7.74 (d, *J* = 8.0 Hz, 2H), 7.54-7.51 (m, 2H), 7.37-7.35 (m, 3H), 7.28-7.25 (m, 6H), 5.52 (br, 1H), 4.89 (s, 2H), 4.30-4.28 (d, *J* = 8.0 Hz, 2H), 4.22-4.19 (m, 2H), 2.59-2.56 (q, *J* = 4.0 Hz, 2H), 2.09 (s, 3H), 2.04-2.01 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 156.4, 143.7, 141.4, 135.1, 129.4, 128.9, 128.6, 127.3, 127.2, 125.3, 120.1, 78.5, 67.4, 51.3, 47.2, 31.6, 30.0, 15.5 ppm; IR (KBr): 3281, 2961, 1698, 1657, 1544, 1294, 1251, 748, 742, 541 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{27}H_{29}N_2O_4S$ 477.1848, found 477.1852.

3.8. Selected Spectra

3.8.1. ^{1}H NMR and ^{13}C NMR of selected compounds

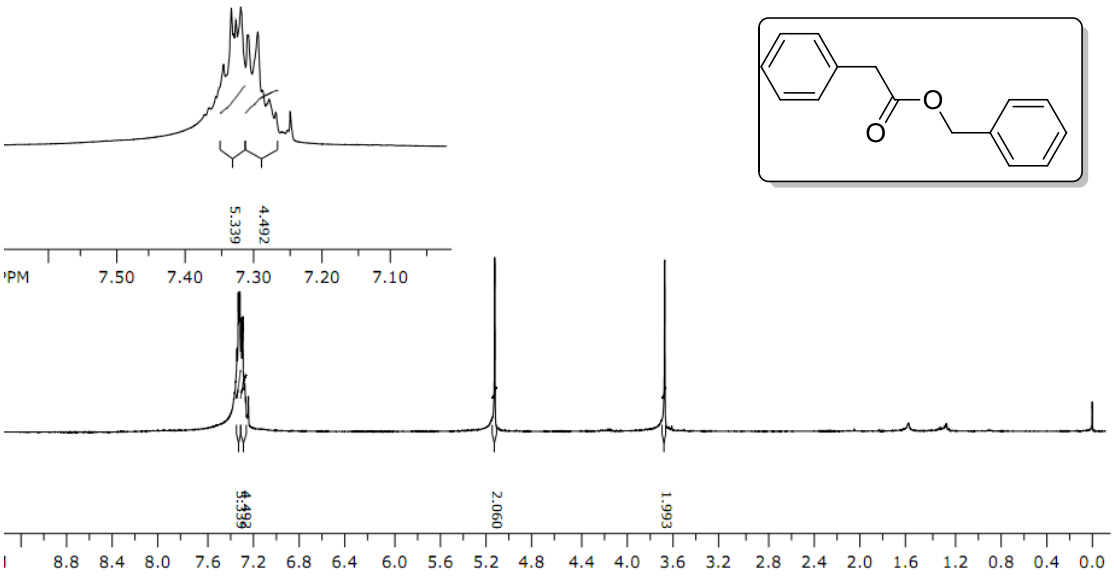


Figure S1: ^{1}H-NMR spectrum of benzyl 2-phenylacetate (entry 5, Table 3.1.2)

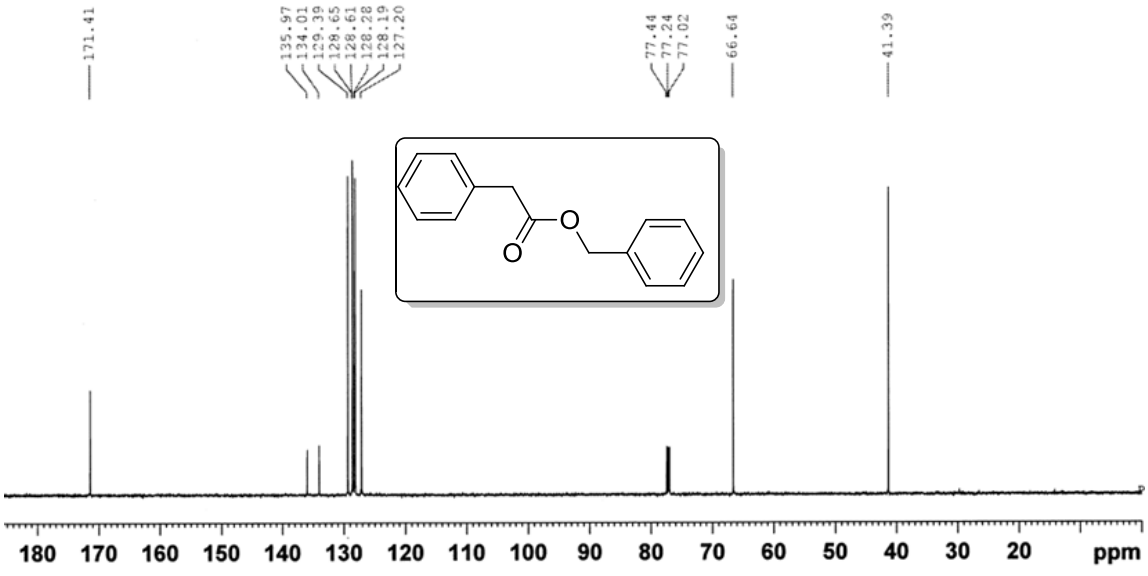


Figure S2: ^{13}C-NMR spectrum of benzyl 2-phenylacetate (entry 5, Table 3.1.2)

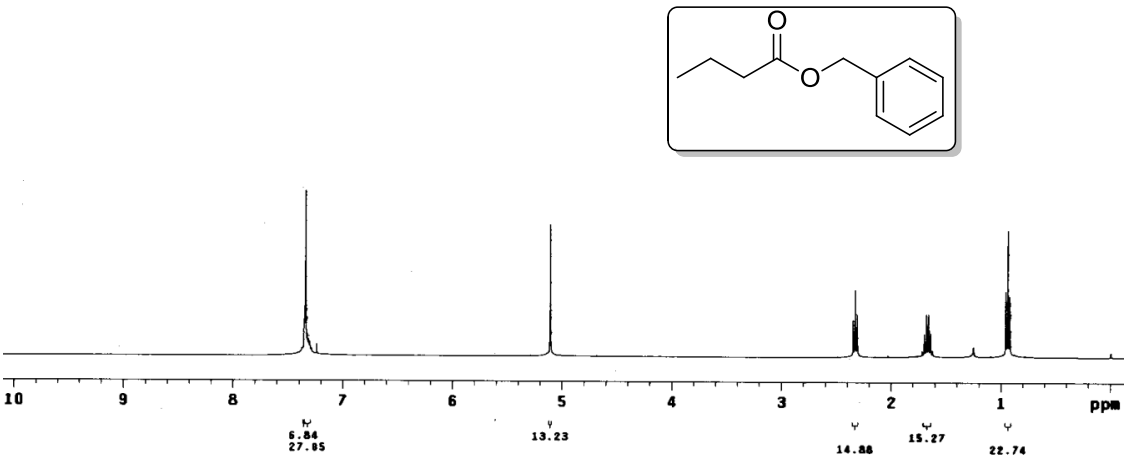


Figure S3: ^{1}H-NMR spectrum of benzyl butyrate (entry 9, Table 3.1.2)

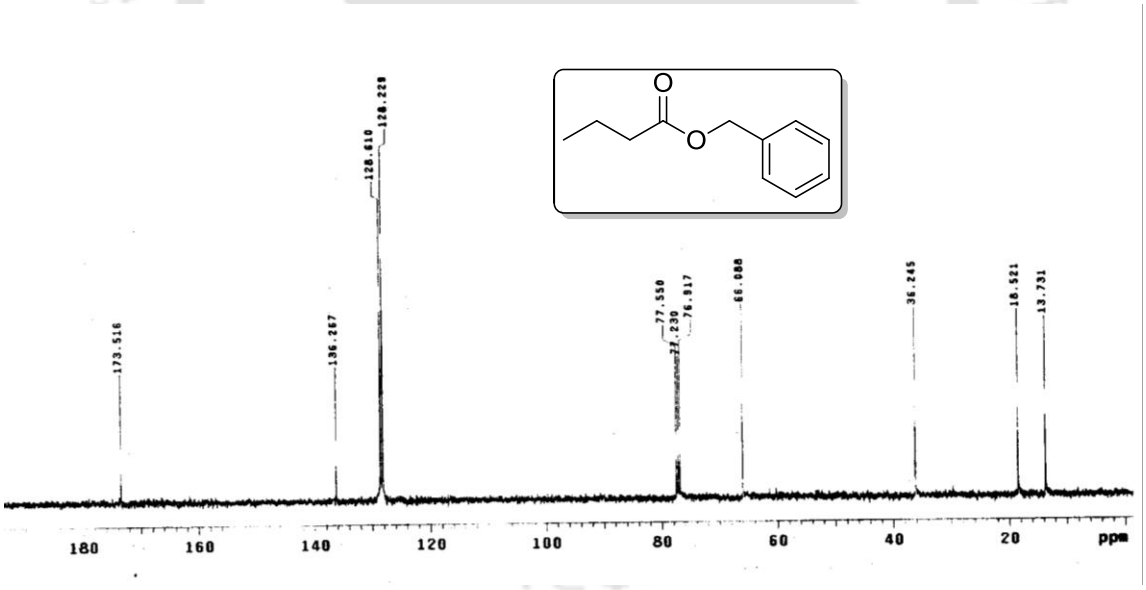


Figure S4: ^{13}C-NMR spectrum of benzyl butyrate (entry 9, Table 3.1.2)

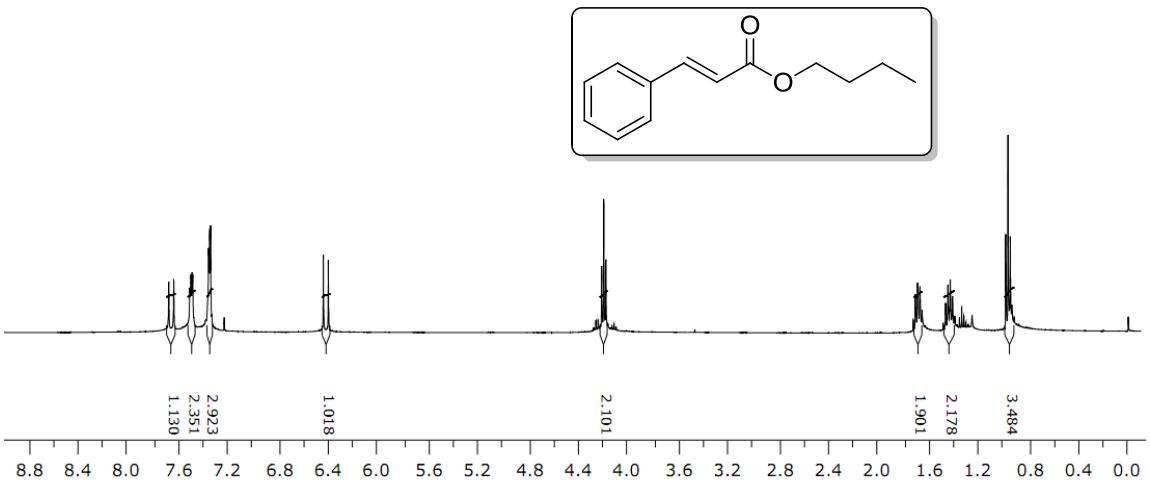


Figure S5: ^{1}H-NMR spectrum of butyl cinnamate (entry 12, Table 3.1.2)

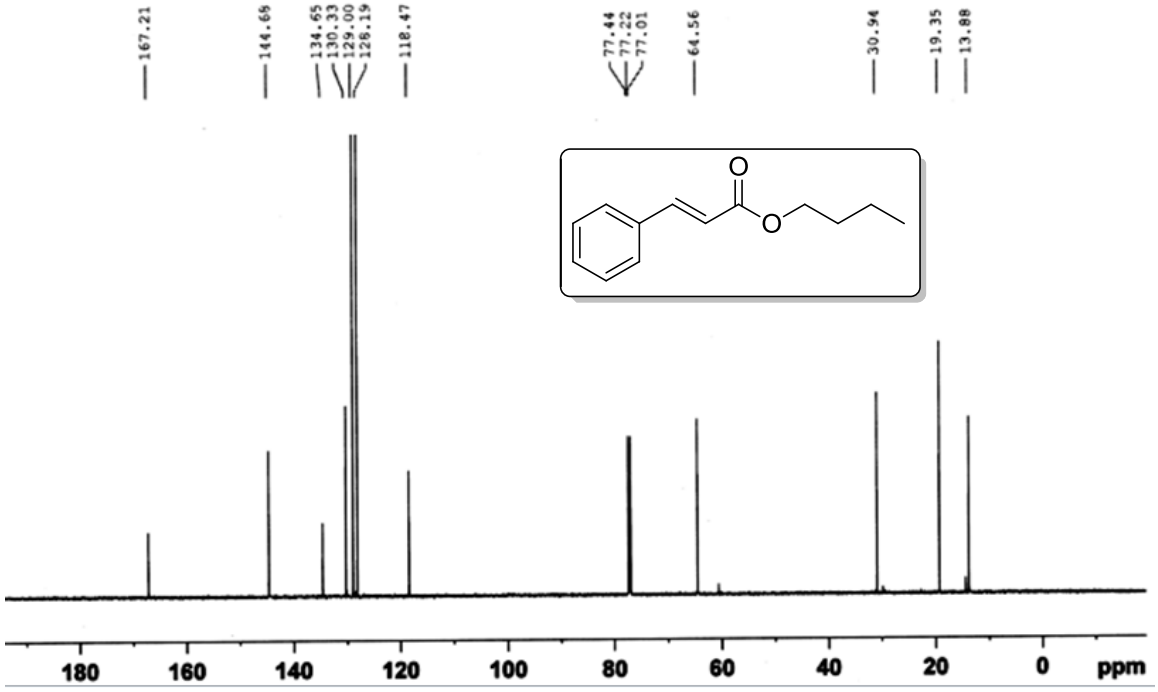


Figure S6: ^{13}C-NMR spectrum of butyl cinnamate (entry 12, Table 3.1.2)

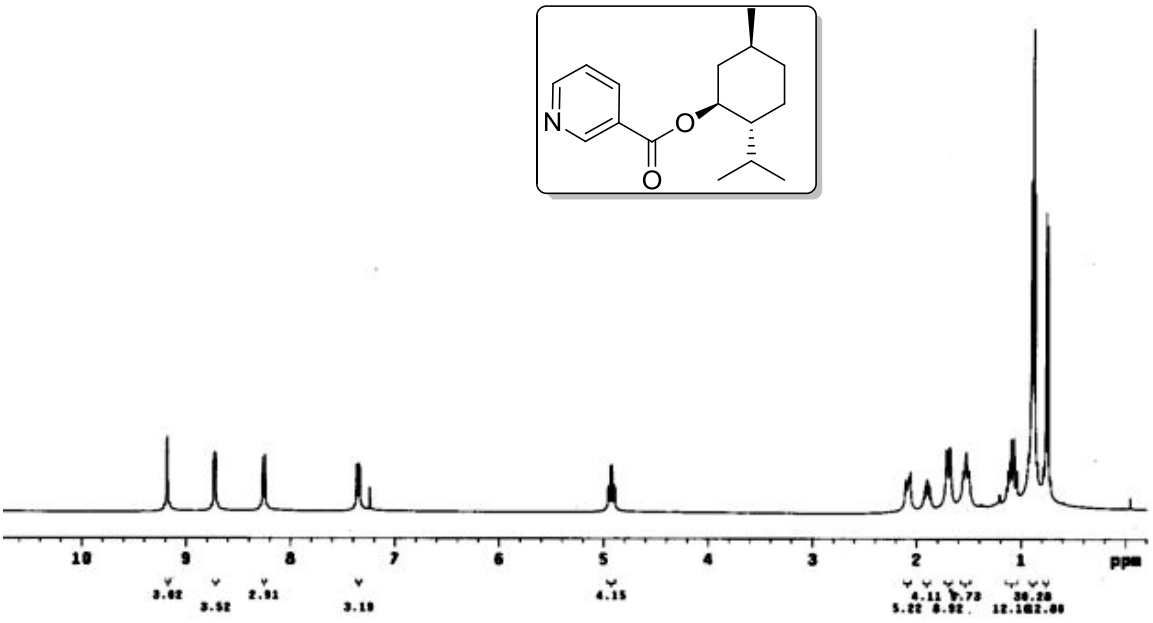


Figure S7: ^{1}H-NMR spectrum of (1S,2R,5S)-2-isopropyl-5-methylcyclohexyl nicotinate (entry 7, Table 3.1.3)

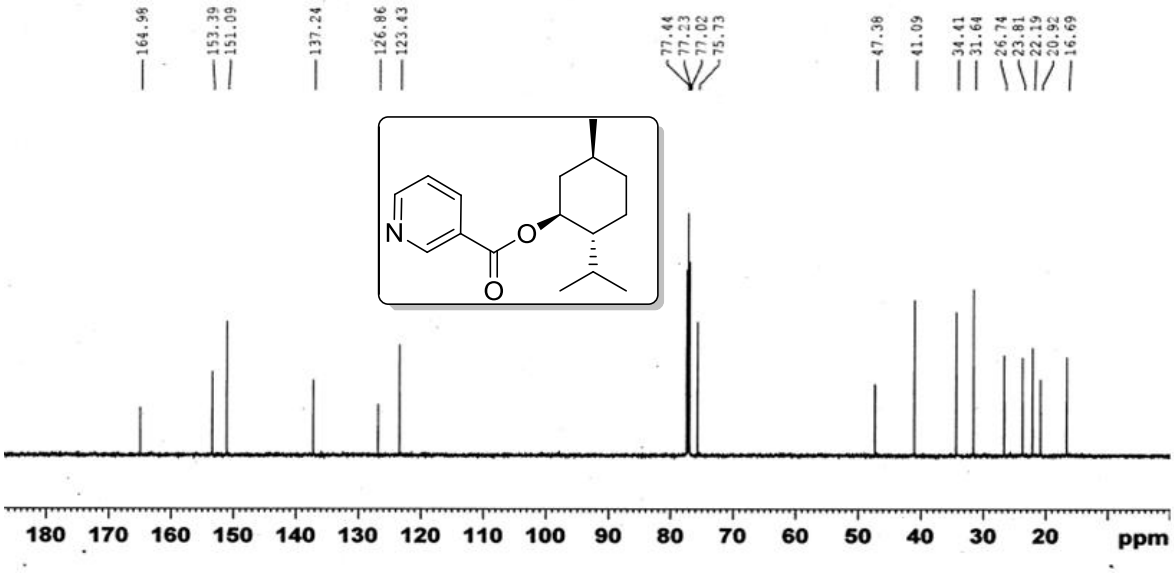


Figure S8: ^{13}C-NMR spectrum of (1S, 2R, 5S)-2-isopropyl-5-methylcyclohexyl nicotinate (entry 7, Table 3.1.3).

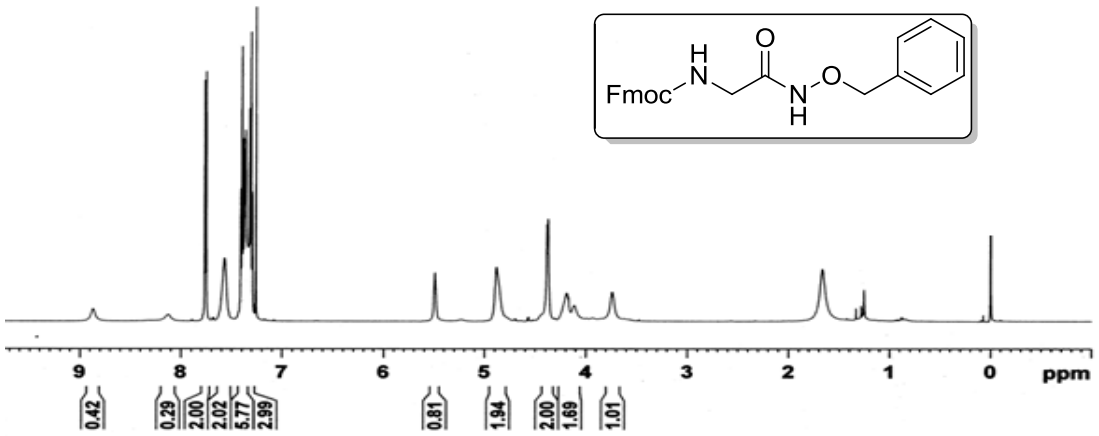


Figure S9: ^{1}H-NMR spectrum of (9H-fluoren-9-yl)methyl 2-(benzyloxyamino)-2-oxoethylcarbamate (entry 4, Table 3.3.1)

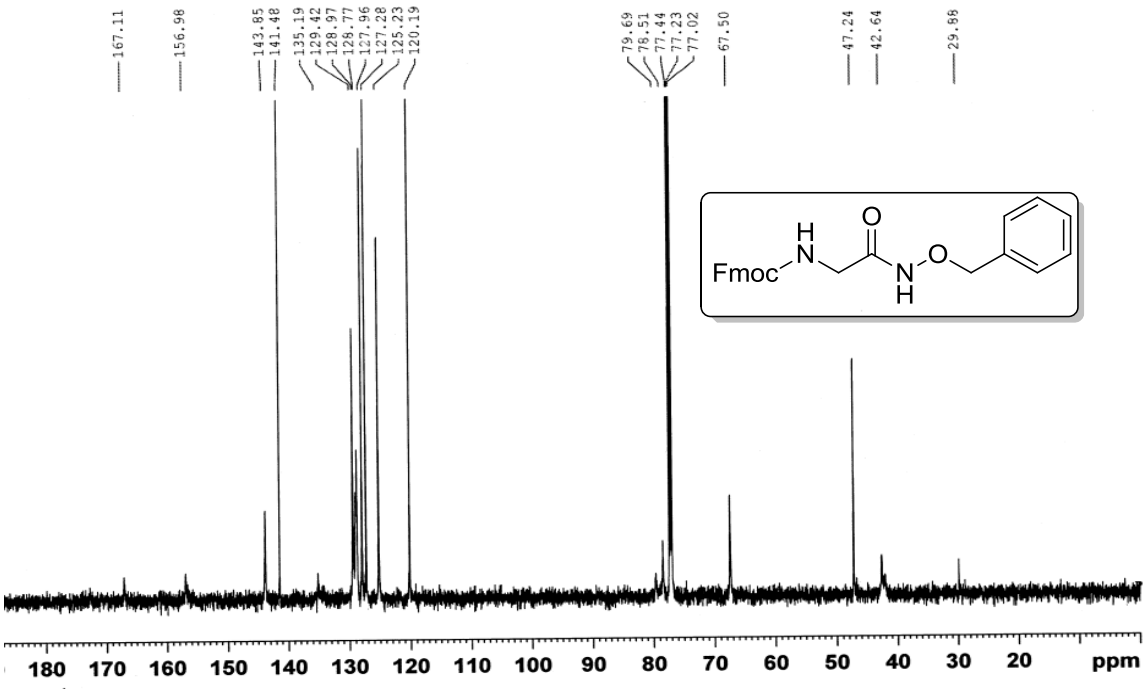


Figure S10: ^{13}C-NMR spectrum of (9H-fluoren-9-yl)methyl 2-(benzyloxyamino)-2-oxoethylcarbamate (entry 4, Table 3.3.1)

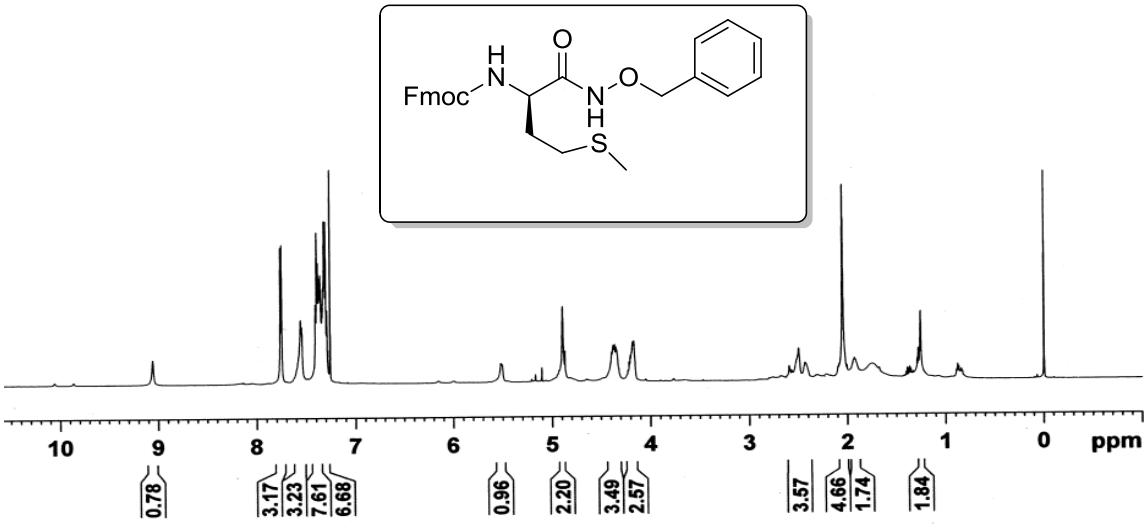


Figure S11: ^{1}H-NMR spectrum of (9H-fluoren-9-yl)methyl 1-(benzyloxyamino)-4-(methylthio)-1-oxobutan-2-ylcarbamate (entry 8, Table 3.3.1)

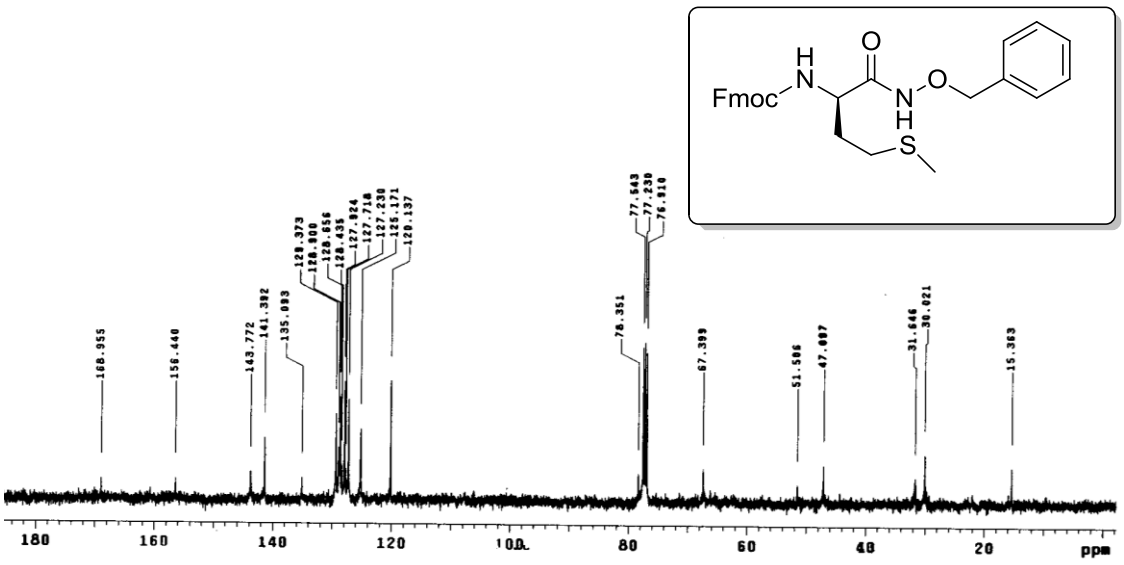


Figure S12: ^{13}C-NMR spectrum of (9H-fluoren-9-yl)methyl 1-(benzyloxyamino)-4-(methylthio)-1-oxobutan-2-ylcarbamate (entry 8, Table 3.3.1)

3.8.2. Data for racemization test

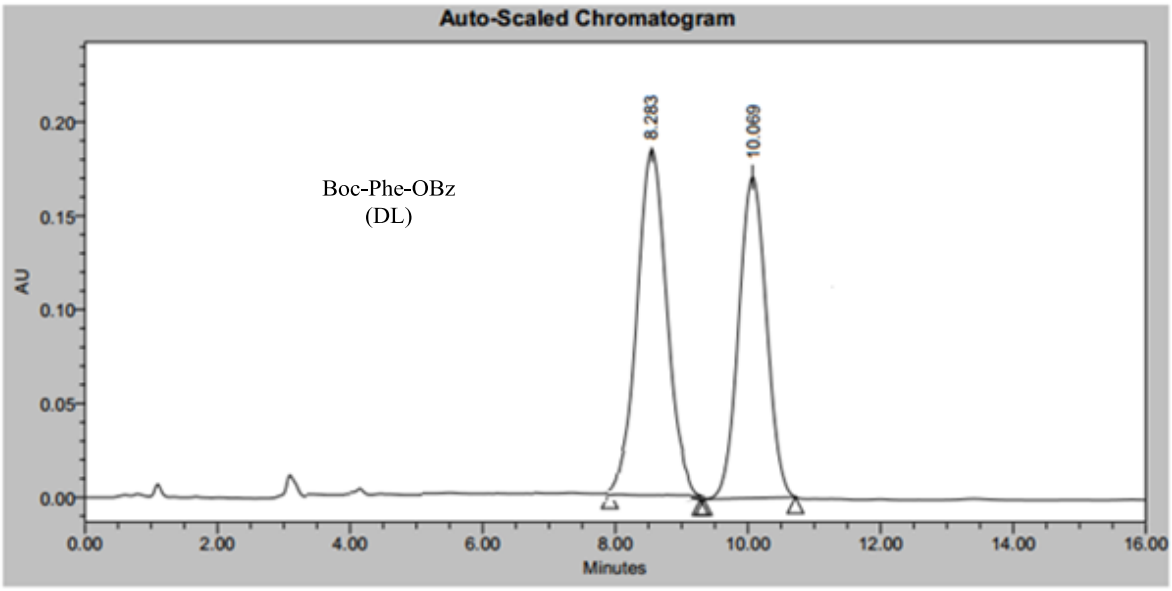


Figure S13: HPLC chromatogram of Boc-DL-Phe-OBz run in CHIRAL PAK^{R} AS-H (5 µm, 2.1×150mm) column in isocratic gradient of 10% isopropanol in hexane (entry 10, Table 3.1.3)

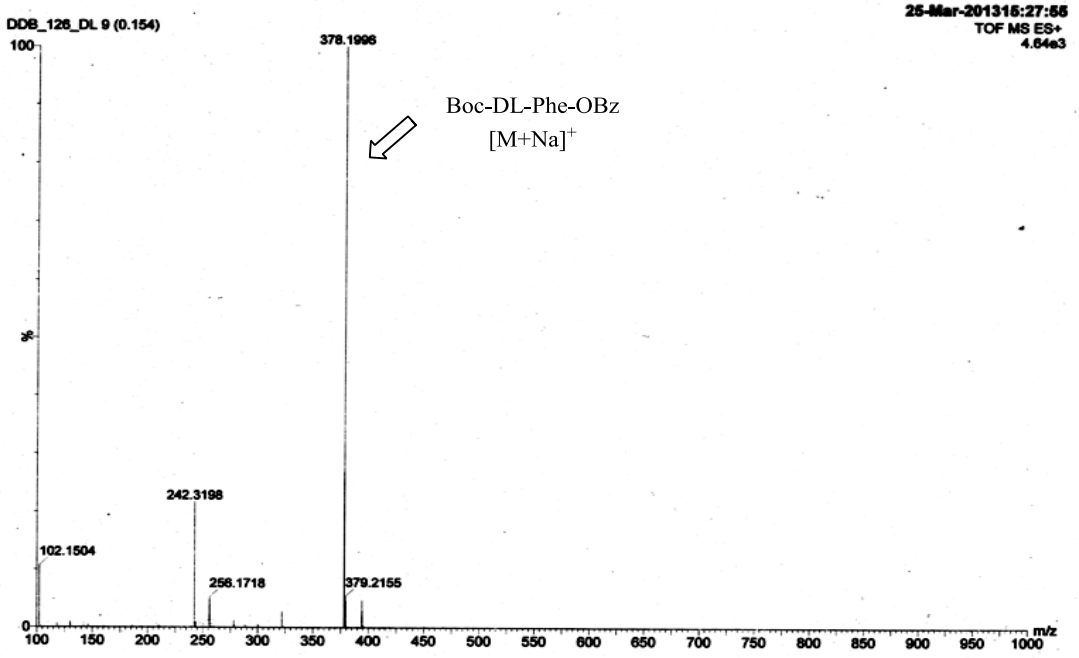


Figure S14: ESI-MS spectrum of Boc-DL-Phe-OBz ester, peak retention time 8.28 min of above chromatogram (entry 10, Table 3.1.3)

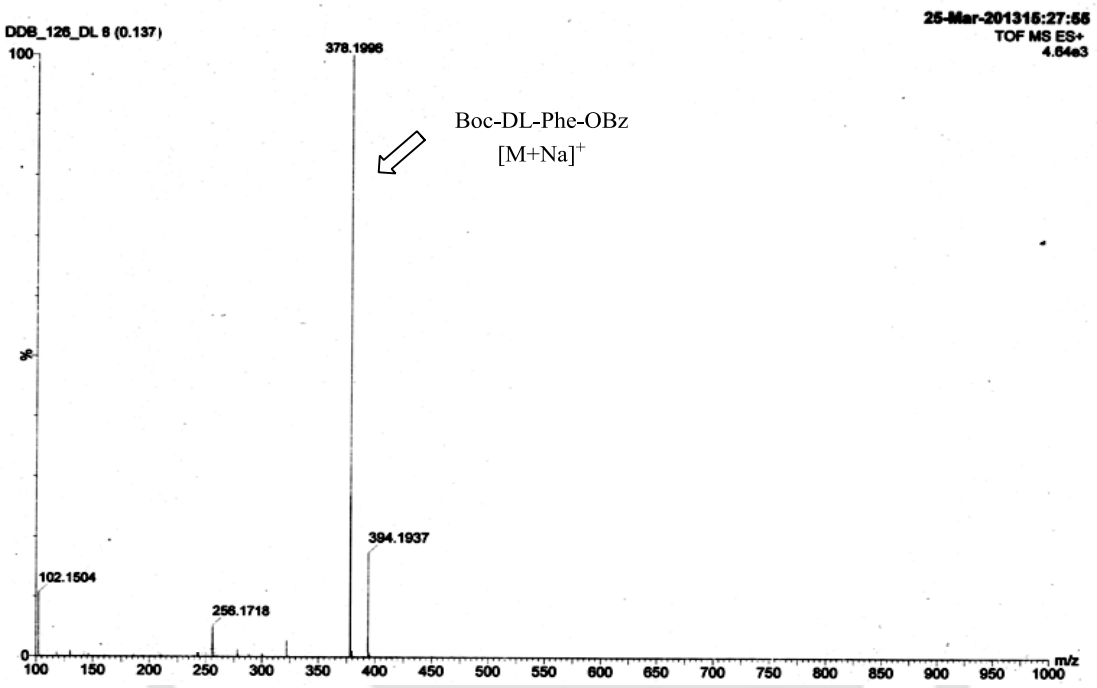


Figure S15: ESI-MS spectrum of Boc-DL-Phe-OBz ester, peak retention time 10.06 min of above chromatogram (entry 10, Table 3.1.3)

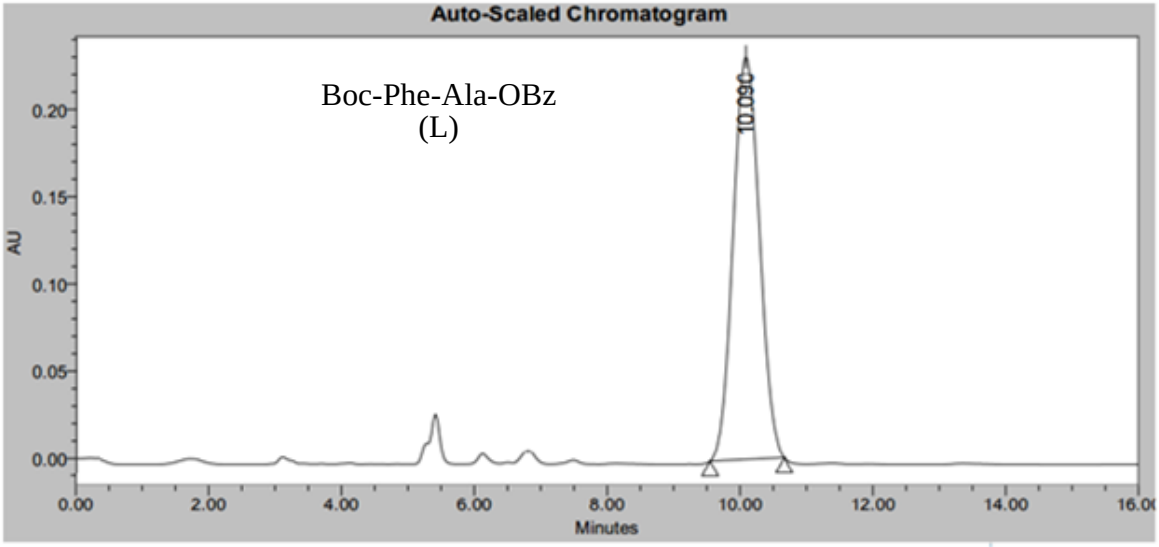


Figure S16: HPLC chromatogram of Boc-L-Phe-OBz runs in CHIRAL PAK^{R} AS-H (5 µm, 2.1×150mm) column in isocratic gradient of 10% isopropanol in hexane (entry 11, Table 3.1.3)

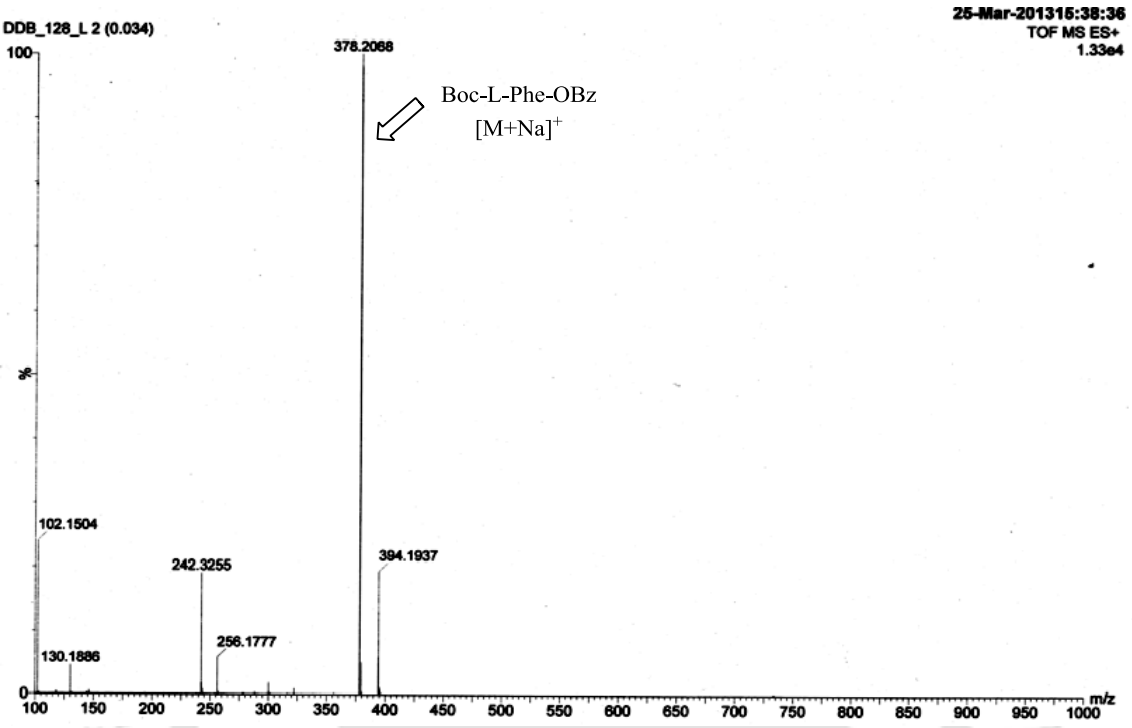
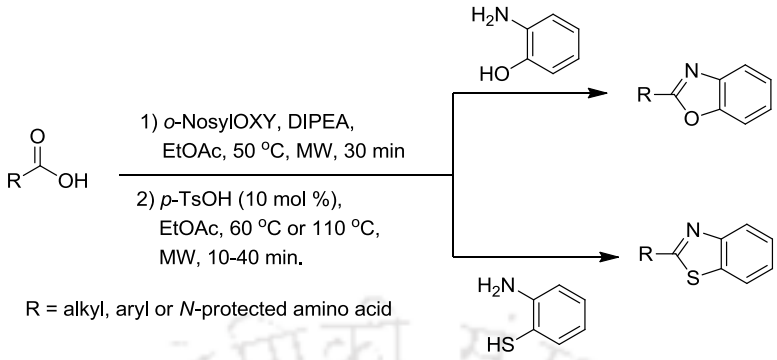


Figure S17: ESI-MS spectrum of Boc-L-Phe-OBz ester, peak retention time 10.09 min of above chromatogram (entry 11, Table 3.1.3)

Chapter 4: Benzoxazole and Benzothiazole Synthesis from Carboxylic Acid in Solution and on Resin using Ethyl 2-cyano-2-(2-nitrobenzenesulfonyl oxyimino) acetate (*o*-NosylOXY) and *p*-TsOH

In continuation of the application of the reagent, ethyl 2-cyano-2-(2-nitrobenzenesulfonyloxy imino)acetate (*o*-NosylOXY, **I**) for the synthesis of amide, peptide, ester, and hydroxamate, in this chapter we wanted to show the application of the reagent for the synthesis of nitrogen containing heterocyclic compound benzoxazole and benzothiazole and their derivatives which are present in many pharmaceutical important compounds with wide spectrum of biological activities (Chapter 1, section 1.3.3). For the synthesis of benzoxazoles and benzothiazoles, several methods are reported. The major disadvantages of the existing methods (Chapter 1, section 1.6) are use of metal catalyst, additive and long reaction time. Here, we developed a metal free method for the synthesis of benzoxazoles and benzothiazoles by the condensation of *o*-aminophenol or *o*-aminothiophenol with *N*-protected amino acid and carboxylic acid using *o*-NosylOXY and *para*-totuenesulfonic acid (*Scheme 4.1*).



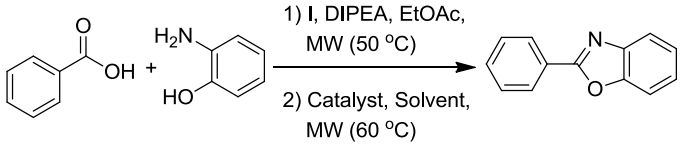
Scheme 4.1. Synthesis of derivative of benzoxazole and benzothiazole

4.1. Reaction optimization and substrate scope of synthesis of benzoxazole and benzothiazole using *o*-NosylOXY (I) and *p*-TsOH (II)

The synthesis of *o*-NosylOXY (**I**) was carried out in a similar manner as described in chapter 2, section 2.1. For a model reaction, we took, equivalent mole of phenylacetic acid, *o*-NosylOXY, and DIPEA were dissolved in ethyl acetate and kept the reaction mixture for pre-activation for 5 min at room temperature, followed by the portion wise addition of *o*-aminophenol. The reaction mixture was then heated under microwave at 50 °C and 80 Watt in a closed vessel. After completion of first step of the reaction (TLC, ~30 min), the reaction mixture was heated again in presence of catalytic amount of *p*-TsOH (10 mol%) for another 10 min at 60 °C and 80 Watt, under microwave in a closed vessel. Product was purified by column chromatography with 92% yield.

For optimization, we took benzoic acid (*entry 1, Table 4.1.2)* as substrate. For solvent optimization of the dehydration step, we screened various solvents, such as toluene, DCM, EtOAc, DMSO, dioxane, CH_3CN, $CHCl_3$, and DMF. Out of these solvents, EtOAc was found to be the best (*Table 4.1.1*). Next, we screened various catalysts and *p*-TsOH was found to be the best at the optimized condition (*entries 8-15, Table 4.1.1*).

Table 4.1.1. Optimization of the reaction conditions[a]

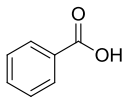
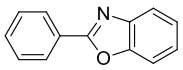
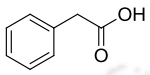
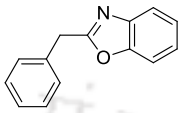
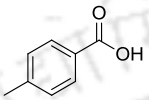
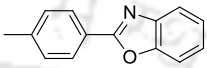
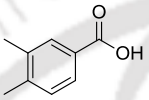
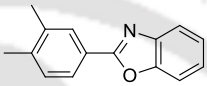
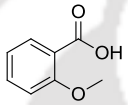
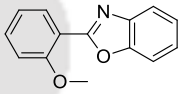
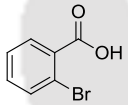
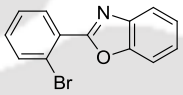
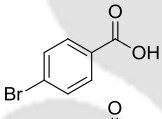
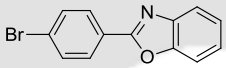
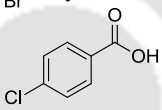
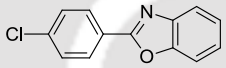
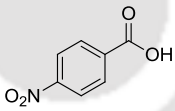
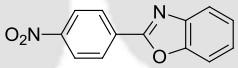
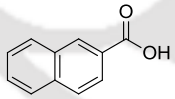
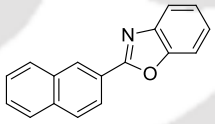
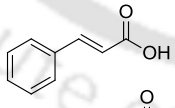
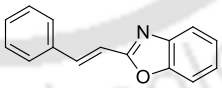
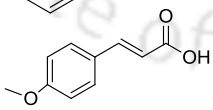
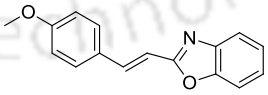
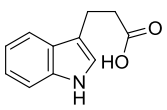
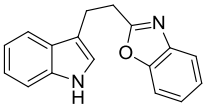
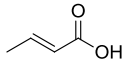
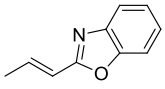


Entry	Catalyst (10 mol %)	Solvent	Time (min.)	Yield (%)[b]
1	*p*-TsOH	Toluene	30	50
2	*p*-TsOH	DMSO	50	10
3	*p*-TsOH	$CHCl_3$	40	0
4	*p*-TsOH	DMF	30	12
5	***p*-TsOH**	**EtOAc**	**10**	**92**
6	*p*-TsOH	THF	30	10
7	*p*-TsOH	Dioxane	20	78
8	*p*-TsOH	Acetonitrile	60	0
9	$CaCl_2$	EtOAc	60	10
10	P_2O_5	EtOAc	40	10
11	$AlCl_3$	EtOAc	20	50
12	$CaSO_4$	EtOAc	25	0
13	CaO	EtOAc	45	0
14	H_3PO_4	EtOAc	50	40
15	$FeCl_3$	EtOAc	30	25

[a]*Performed with benzoic acid (1 equiv), o-NosylOXY (1 equiv), DIPEA (1 equiv), and o-aminophenol (1 equiv) under microwave irradiation (upper limit was fixed at 80 Watt).* [b]*Yields were referred to the isolated yields after column chromatography.*

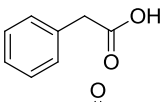
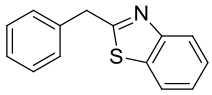
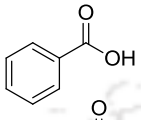
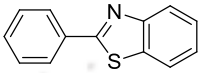
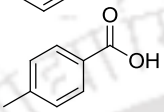
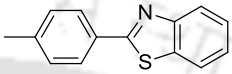
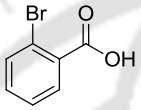
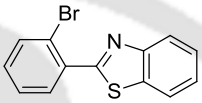
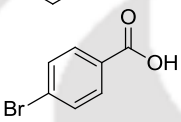
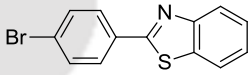
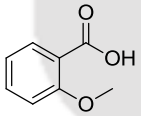
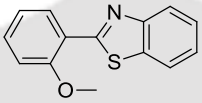
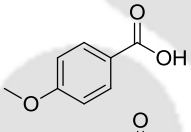
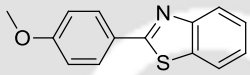
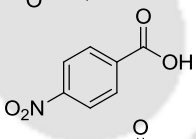
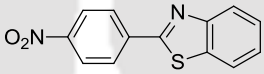
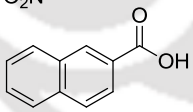
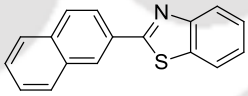
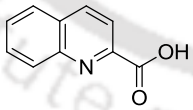
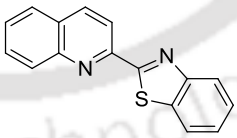
Further, to explore the scope of this methodology, we synthesized various derivatives of benzoxazole (*Table 4.1.2*) and benzothiazole (*Table 4.1.3*) using the optimized condition. The current methodology tolerates variety of functional group, for example methoxy, methyl, nitro, chloro, and bromo. All the substrates underwent the reaction to furnish the desired products with 81-92% yields.

Table 4.1.2. Synthesis of various benzoxazoles[a]

Entry	Carboxylic acid	Product	Yield (%)[b]
1			92
2			92
3			89
4			88
5			81
6			90
7			85
8			87
9			89
10			90
11			91
12			87
13			87
14			85

[a]*Performed with carboxylic acid (1 equiv), o-NosylOXY (1 equiv), DIPEA (1 equiv), o-aminophenol (1 equiv), and catalyst II (10 mol%) under microwave for 10 min.* [b]*Yields were referred to the isolated yields after column chromatography.*

Table 4.1.3. Synthesis of benzothiazoles[a]

Entry	Carboxylic acid	Product	Yield (%)[b]
1			92
2			90
3			89
4			88
5			89
6			91
7			90
8			81
9			88
10			85

[a]*Performed with carboxylic acid (1 equiv), o-NosylOXY (1 equiv), DIPEA (1 equiv), o-aminothiophenol (1 equiv), and reagent II (10 mol %) under microwave irradiation for 10 min.* [b]*Yields were referred to the isolated yields after column chromatography*

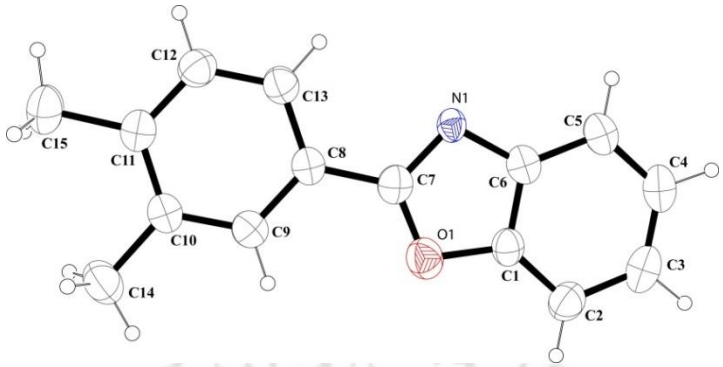
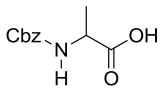
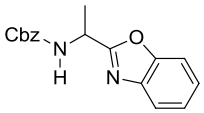
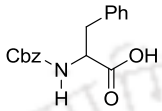
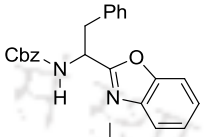
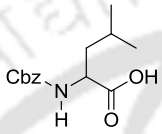
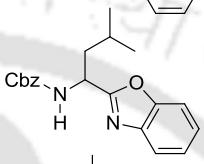
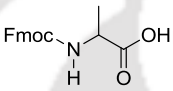
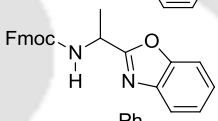
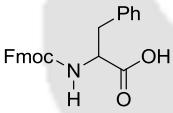
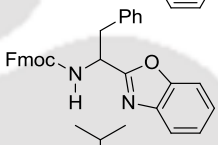
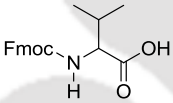
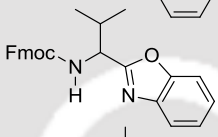
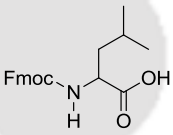
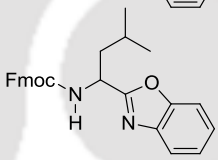
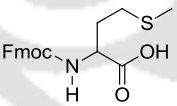
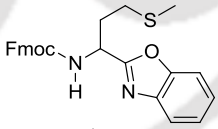
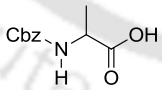
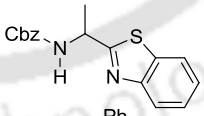
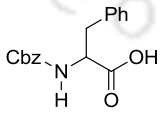
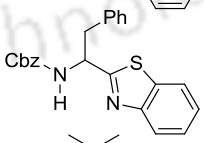
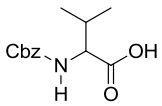
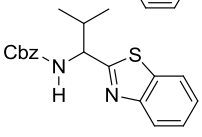
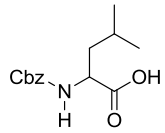
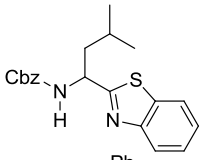
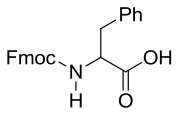
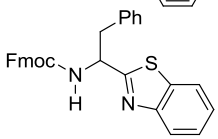
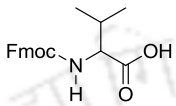
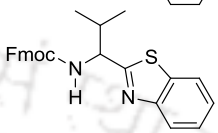


Figure 4.1.1. X-ray crystallographic structure of the product (*entry 4, Table 4.1.2*) (ORTEP diagram with ellipsoid of 30% probability, CCDC No. 1422635).

After obtaining the excellent yields with simple carboxylic acids, we tried to explore the application of methodology for the synthesis of benzoxazole and benzothiazole of *N*-protected amino acids. We took equivalent amount of Cbz-Alanine and *o*-NosylOXY with DIPEA in ethyl acetate, and treated under previously optimized condition, but the reaction was unsuccessful. Then we went to further optimize the reaction condition and tried various catalysts, solvents and temperatures. Finally, we found that with increasing the reaction temperature to 110 °C (other parameters were same as before), the reaction worked well with reasonably good yields. Next, we synthesized various derivatives of benzoxazoles and benzothiazoles of Cbz-protected (*entries 1-3 and 9-12, Table 4.1.4*) and Fmoc-protected amino acids (*entries 4-8 and 13-14, Table 4.1.4*) with 61-72% yields under optimized condition. The yields of table 4.1.2 and 4.1.3 are better than table 4.1.4 due to the aromatic carboxylic acids which form resonance stabilize product.

Table 4.1.4. Synthesis of benzoxazole and benzothiazole of *N*-protected amino acid[a]

Entry	*N*-protected amino acid	Product	Yields (%)[b]
1			70
2			72
3			67
4			67
5			71
6			64
7			65
8			66
9			61
10			68
11			63

12			65
13			69
14			62

[a]*Performed with N-protected amino acid (1 equiv), reagent I (1 equiv), DIPEA (1 equiv), o-aminophenol or o-aminothiophenol (1 equiv) for 30 min and catalyst II (10 mol%) under microwave irradiation for 30-40 min.* [b]*Yields were referred to the isolated yields after column chromatography.*

After successful synthesis of the benzoxazoles and benzothiazoles of *N*-protected amino acids in solution phase, we extended the methodology further for the synthesis of benzoxazoles on solid support. We have synthesized benzoxazole derivatives of two biologically active molecules, $hIAPP_{22\text{-}27}$ (human islet amyloid polypeptide, *Scheme 4.1.1*), which is known to be the core sequence responsible for the initiation of aggregation of the amylin peptide that leads to type 2 diabetes and $A\beta_{18\text{-}21}$ (amyloid β, *Figure 4.1.2*) that is known as key sequence of Aβ aggregation responsible for Alzheimer's disease. Both are known as difficult sequence for solid phase peptide synthesis (SPPS).

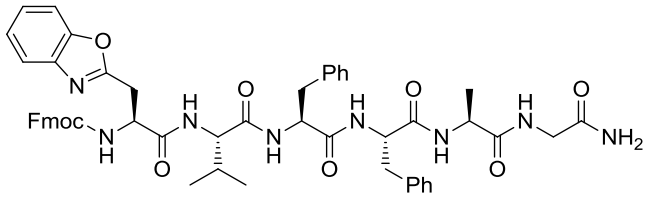
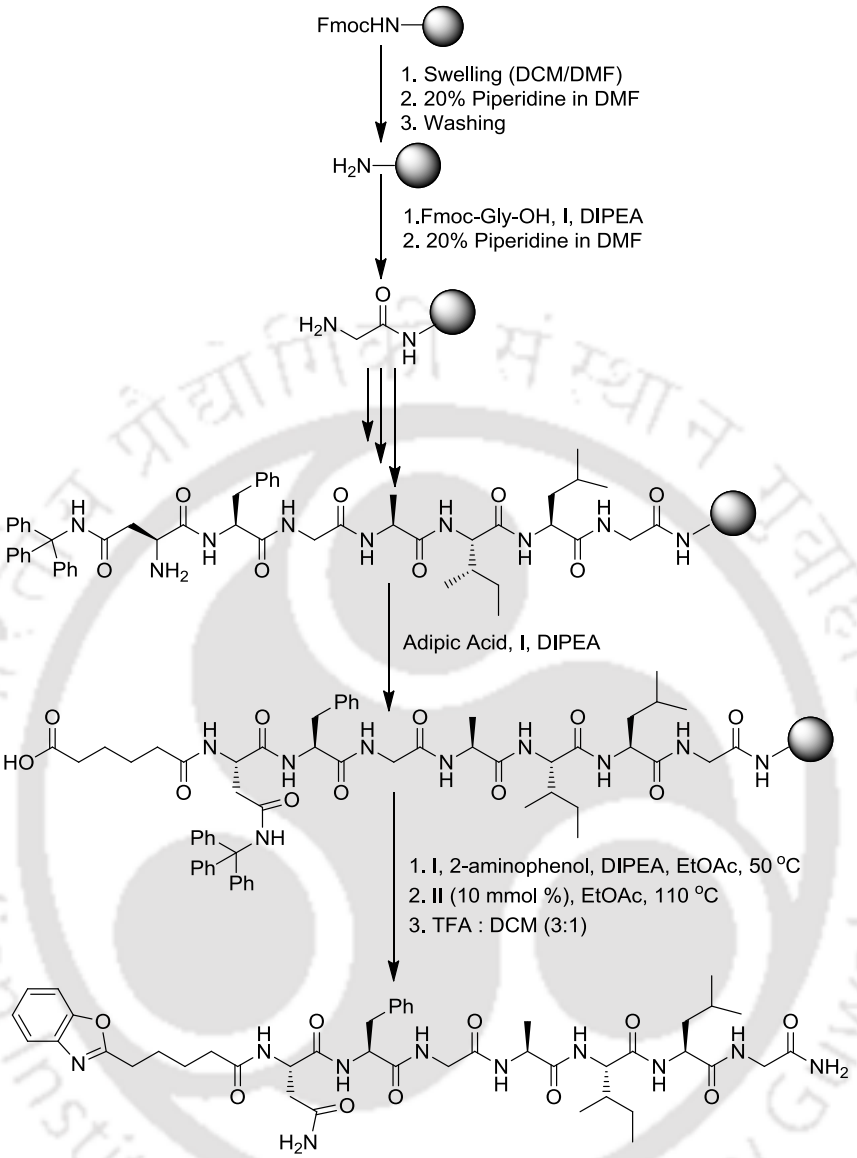


Figure 4.1.2. Benzoxazole derivative of side chain of aspartic acid of Fmoc-DVFFAG-NH_2



Scheme 4.1.1. Synthesis of benzoxazole of adipoyl hIAPP$_{22-27}$ (NFGAILG) using Fmoc/^{t}Bu protection strategy

For the synthesis of benzoxazole of hIAPP$_{22-27}$, we first synthesized hIAPP$_{22-27}$ on Rink Amide MBHA resin using Fmoc/^{t}Bu based SPPS chemistry. Then, we attached an adipic acid at the *N*-terminal of hIAPP$_{22-27}$ and the attachment was confirmed by HPLC and ESI-MS (*Figure S9 and S10*). Further, the free carboxylic acid of adipic acid was coupled with *o*-aminophenol (3 equiv) in presence of reagent I (3.5 equiv) and DIPEA (4 equiv) at

50 °C in microwave on solid support. Special feature of this synthesis was, all the coupling reactions including the coupling of *o*-aminophenol could be performed by reagent *o*-NosylOXY. Finally, cyclization was performed in presence of *p*-TsOH (10 mol%) at 110 °C under microwave on resin. Final product was cleaved from the resin using the cocktail solution TFA/DCM/H_2O (9/0.5/0.5) for nearly 3 h. The cleaved product was precipitated by cold diethyl ether and centrifuged to get crude solid product. The crude product was purified by semi-preparative HPLC and characterized by ESI-MS (*Figure S11 and S12*). Another interesting feature was that the yield of the peptide was good (59% crude and 21% after purification by HPLC w.r.t. resin loading) indicating practically no significant loss despite of using *p*-TsOH and temperature as high as 110 °C on acid labile Rink Amide MBHA resin.

Similarly, for the synthesis of benzoxazole derivative of $A\beta_{18\text{-}21}$, first we attached a Fmoc-(O^{t}Bu)Asp-OH at the *N*-terminal of VFFAG by above described method on solid support. Then the side chain protecting group, ^{t}Bu of Fmoc-Asp(O^{t}Bu)-OH was de-protected by $ZnCl_2$/DCM in 48 h on solid support (*Figure S13 and S14*). Then the generated side chain carboxylic acid of aspartic acid residue was coupled with *o*-aminophenol (3 equiv) using reagent *o*-NosylOXY (3.5 equiv) and DIPEA (4 equiv) at 50 °C in microwave, after that cyclization was performed with *p*-TsOH (10 mol%) at 110 °C in microwave. Final product was cleaved from the resin using the cocktail of TFA/DCM/H_2O (9/0.5/0.5) for nearly 3 h. The final product was purified by semi-preparative HPLC and characterized by ESI-MS (*Figure S15 and S16*). Yield of the crude peptide was 54% (16% w.r.t. the resin loading after purification by semi-preparative HPLC). The Gly residue was attached at the *C*-terminal of both the peptides to serve as

spacer. Thus, the syntheses of benzoxazole derivatives of biologically important peptides were achieved on solid support.

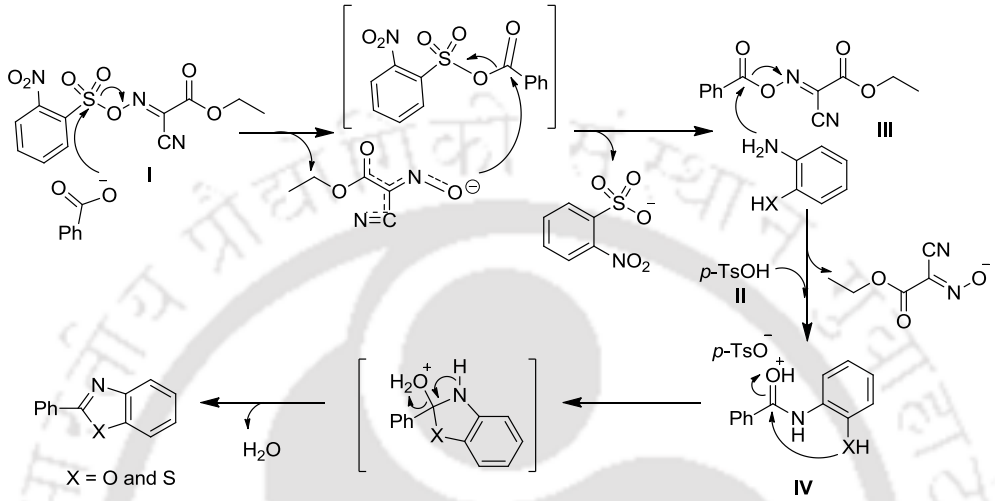
4.2. Racemization study

For investigation of racemization, we synthesized benzoxazole derivatives of tripeptides, Z-(L)Ala-(DL)Phe-Gly-OH and Z-(L)Ala-(L)Phe-Gly-OH, by using the solution phase method. We obtained the desired products easily, indicating C-terminal attachment of benzoxazole and benzothiazole is also feasible by this method. To estimate the amount of racemization, we compared the HPLC profiles (*Figures S17–S27*). The appearance of the twin peaks in the HPLC profile of the benzoxazole of Z-(L)Ala-(DL)Phe-Gly-OH corresponds to the two diastereomeric products as expected. Careful analysis of the HPLC profile of the benzoxazole derivative of Z-(L)Ala-(L)Phe-Gly-OH indicated about 5% racemization.

4.3. Mechanistic study

A plausible mechanism for the synthesis of benzoxazole and benzothiozole is depicted in scheme 4.3.1. First, the carboxylic acid gets deprotonated by DIPEA that attacks the electrophilic center of the reagent **I** to form the active ester of Oxyma (ethyl 2-cyano-2-(hydroxyimino)acetate, **III**), followed by attacks of amine group of *o*-aminophenol or *o*-aminothiophenol to the electrophilic center of **III** to form the stable amide intermediate IV. The intermediates **III** and **IV** were characterized by ^{1}H NMR and ^{13}C NMR (*Figure S1-S4*), mass spectrometry and FT-IR. Further, intramolecular cyclization of the amide

intermediate **IV** and subsequent dehydration generates the final product in presence of catalytic amount of *p*-TsOH under MW irradiation.



Scheme 4.3.1. A plausible mechanism for condensation and subsequent cyclization

4.4. Conclusions

We synthesized substituted benzoxazole and benzothiozole by using ethyl 2-cyano-2-(2-nitrobenzenesulfonyloxy imino) acetate (*o*-NosylOXY) and catalytic amount of *p*-TsOH (10 mol%) under microwave with good yield. Benzoxazole and benzothiazole derivatives of *N*-protected amino acids were also synthesized in solution phase. Most importantly, syntheses of benzoxazole derivatives of oligopeptides via SPPS were also demonstrated. Reactions worked well both in solution phase and on solid supported resin. A plausible mechanism was also described, and intermediates were characterized. Two medicinally important products were synthesized using this method (*entries 5 and 7, Table 4.1.2*).[126a]

4.5. Experimental Section

4.5.1. General consideration

As described in chapter 2, section 2.6.1 and elemental analysis was carried out with a Vario EL III Elementor.

4.5.2. General procedure for the synthesis of benzoxazoles and benzothiazoles

DIPEA (1 equiv) was added to a solution of the carboxylic acid (1 equiv) and *o*-NosylOXY (1 equiv) in EtOAc. After 5 min preactivation, *o*-aminophenol or *o*-aminothiophenol (1 equiv) was added to the reaction mixture and stirred for 30 min. at 50 °C in a microwave in a close vessel. After completion of first step, *p*-TsOH (10 mol%) was added to it, and kept for another 10 min at 60 °C in microwave. After completion of the reaction, the reaction mixture was diluted with ethyl acetate (5 mL) and washed with 5% $NaHCO_3$ (3 times). Finally reaction mixture was dried over Na_2SO_4 and product was purified by column chromatography.

4.5.3. General procedure for the synthesis of benzoxazoles and benzothiazoles of *N*-protected amino acid

In solution *N*-protected amino acid (1 equiv) and *o*-NosylOXY (1 equiv) in EtOAc, DIPEA (1 equiv) was added. After 5 min preactivation *o*-aminophenol or *o*-aminothiophenol (1 equiv) was added to the reaction mixture and stirred for 30 min at 50 °C in a microwave in a close vessel. After completion of first step, *p*-TsOH (10 mol%) was added in the reaction mixture, and kept for another 30-40 min at 110 °C in the microwave. After completion of the reaction, the reaction mixture was diluted with ethyl

acetate (5 mL) and washed with 5% $NaHCO_3$ (3 times). Finally organic layer was dried by Na_2SO_4 and product was purified by column chromatography.

4.5.4. General procedure for the synthesis of benzoxazoles on solid supported resin

4.5.4.1. Synthesis of benzoxazole of Adipoyl-NFGAILG-NH_2

Peptide was synthesized following the Fmoc/^{t}Bu strategy on solid supported Fmoc-Rink Amide MBHA (loading, 0.7 mmol/g) resin. The syntheses were performed manually on a Stuart blood tube rotator. The resin was taken into a 5 mL frit-fitted plastic syringe and swollen in DCM for 2 h followed by DMF for 1 h. The solution of Fmoc-amino acid (3.0 equiv), *o*-NosylOXY (3.5 equiv) and DIPEA (5 equiv) was kept for preactivation for 5 min. Then this solution was added to the Fmoc deprotected swelled resin, coupling was completed in 2 h. The deprotection-acylation cycle was continued as required. Then final peptide was connected with adipic acid. After that, the adipic acid connected peptide was taken in microwave reaction tube and *o*-NosylOXY (3.5 equiv) and DIPEA (4 equiv) were added, kept for 5 min for preactivation in EtOAc followed by addition of *o*-aminohenol (3 equiv) at 50 °C, 80 W in microwave reactor for 30 min. Washed with EtOAc, then *p*-TsOH (10 mol%) was added in the same reaction mixture and kept at 110 °C, 80 W for 30 min in microwave. After completion of the reaction, the resin was washed with DCM. Peptide was cleaved from the resin using the cocktail solution TFA/DCM/H_2O (9/0.5/0.5) for nearly 3 h. Purification of the peptide was performed using semi-preparative HPLC using a linear gradient over 20 min (5 to 100% CH_3CN in H_2O with 0.09% TFA) and characterized ESI-MS, $[M+H]^+$ = 991.5 (*Figure S11-S12*).

4.5.4.2. Synthesis of benzoxazole of side chain of aspartic acid in Fmoc-DVFFAG-NH_2

The peptide, Fmoc-DVFFAG-NH_2, was synthesized in a similar fashion as described in the last section (Section 4.5.3.1). After obtaining the final Fmoc-DVFFAG peptide, it was treated with $ZnCl_2$ (5 equiv) to deprotect the ^{t}Bu in Fmoc-Asp-(O^{t}Bu)-OH in DCM for 48 h on solid support. After deprotection of ^{t}Bu, the peptide was taken in microwave reaction vessel and into that, *o*-NosylOXY (3.5 equiv) and DIPEA (4 equiv) were added, the reaction mixture then kept 5 min for preactivation in EtOAc, followed by addition of *o*-aminohenol (3 equiv) at 50 °C, 80 W in microwave for 30 min. Washed with EtOAc, then *p*-TsOH (10 mol%) was added in same reaction mixture and kept at 110 °C, 80 W for 30 min in microwave. After completion of reaction, resin was washed with DCM and the peptide was cleaved from the resin using the cocktail solution TFA/DCM/H_2O (9/0.5/0.5) for nearly 3 h. Purification of the peptide was performed using semi-preparative HPLC using linear gradient of 20 min (40 to 100%, 0-10 min. then 100% CH_3CN up to 20 min in H_2O with 0.09% TFA) and characterized using ESI-MS, $[M+H]^+$ = 949.6 (*Figure S15-S16*).

4.5.5. General procedure for the synthesis of benzoxazole derivatives of Z-(L)Ala-(DL)Phe-Gly-OH and Z-(L)Ala-(L)Phe-Gly-OH

For the synthesis of benzoxazole derivatives of Z-(L)Ala-(DL)Phe-Gly-OH and Z-(L)Ala-(L)Phe-Gly-OH, Boc-Phe-OH (1 equiv) and *o*-NosylOXY (1 equiv) were taken in a 25 mL round-bottom flask, after that, DIPEA (1.2 equiv) was added and the mixture was preactivated for 5 min. In another oven-dried 50 mL round-bottom flask, the methyl ester of glycine (1.5 equiv) was taken in DCM and DIPEA was added to it until a basic

pH was reached. This solution was added to the first round-bottom flask and stirring was continued until completion of the reaction. Then, the reaction mixture was diluted with EtOAc (20 mL), washed with 5% $NaHCO_3$ solution (2×5 mL) and 5% citric acid solution (2×5 mL). Finally, the combined organic layer was dried by using anhydrous Na_2SO_4. A solid product (Boc-Phe-Gly-OMe) was obtained after evaporation of EtOAc by rotary evaporator.

Boc-Phe-Gly-OMe was added to a 50 mL round-bottom flask along with 70% TFA solution in DCM and this mixture was stirred for 2.5 h. After that, the TFA was evaporated by rotary evaporator, and the remaining mixture washed 3 times with diethyl ether to obtain solid Phe-Gly-OMe. The Phe-Gly-OMe then coupled with Cbz-Ala-OH by following the above-mentioned procedure to get Cbz-Ala-Phe-Gly-OMe.

For methyl ester de-protection, lithium hydroxide (1.2 equiv) was added to a solution of Cbz-Ala-Phe-Gly-OMe in THF/H_2O (9:1) at 0 °C and stirred until completion of the reaction. Then, the THF was evaporated by rotary evaporator and the reaction mixture was acidified to pH ~3-4. Then, the reaction mixture was extracted with ethyl acetate. Finally, the ethyl acetate solution was dried over anhydrous Na_2SO_4 and the product was purified by column chromatography.

Finally, Cbz-Ala-Phe-Gly-OH, *o*-NosylOXY, and DIPEA (1 equiv each) were mixed in EtOAc. After 5 min of preactivation, *o*-aminophenol was added to the reaction mixture and stirred for 30 min at 50 °C in a closed vessel in the microwave. After completion of the first step, *p*-TsOH (10 mol%) was added to the reaction mixture, which was heated for another 30-40 min at 110 °C in the microwave. After completion of the reaction, the reaction mixture was diluted with ethyl acetate (5 mL) and washed with 5% $NaHCO_3$ (3

times). Finally, the organic layer was dried over Na_2SO_4 and the product was purified by column chromatography. Products were characterized by ^{1}H NMR and ^{13}C NMR spectroscopy, ESI-MS, and FTIR spectroscopy.

4.5.6. Procedure for synthesis of (E)-Ethyl 2-[(benzoyloxy)imino]-2-cyanoacetate (Intermediate III, Scheme 4.3.1)

In a solution of benzoic acid (1 equiv) and *o*-NosylOXY (1 equiv) in DCM, DIPEA (1 equiv) was added at room temperature and stirring continue. After 1 h, reaction mixture was diluted with 10 mL DCM and washed with 5% $NaHCO_3$ solution and 5% solution of HCl. Finally, the reaction mixture was dried with fused $CaCl_2$ and purified by column chromatography. Reddish solid; R_f = 0.50 (EtOAc:Hexane, 2.0:8.0); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.20 (d, *J* = 8.2 Hz, 2H), 7.71 (t, *J* = 7.2 Hz, 1H), 7.56 (t, *J* = 6.0 Hz, 2H), 4.52 (q, *J* = 6.0 Hz, 2H), 1.45 ppm (t, *J* = 6.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 160.9, 157.2, 135.4, 131.9, 130.8, 129.4, 125.9, 107.2, 64.8, 14.2 ppm; IR (KBr): 3105, 2978, 2230, 1745, 1542, 926, 762, 512 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{12}H_{11}N_2O_4$ 247.0714, found 247.0711.

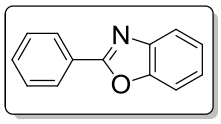
4.5.7. Procedure for synthesis of *N*-(2-Hydroxyphenyl)benzamide (Intermediate IV, Scheme 4.3.1)

The intermediate **III** and *o*-aminophenol (1 equiv) were taken in EtOAc at room temperature and kept for stirring for 2 h. After that the reaction mixture was diluted with 10 mL EtOAc and washed with 5% HCl solution (3 times). Finally organic layer dried with Na_2SO_4 and purified by column chromatography. Yellowish solid: R_f = 0.50 (EtOAc:Hexane, 2.0:8.0); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.25 (s, 1H), 7.88 (d, *J* = 8.2

Hz, 2H), 7.57 (t, *J* = 6.0 Hz, 1H), 7.50 (d, *J* = 6.0 Hz, 2H), 7.28 (d, *J* = 7.8 Hz, 1H), 7.14 (t, *J* = 6.0 Hz, 1H), 7.04 (d, *J* = 8.4 Hz, 1H), 6.90 ppm (t, *J* = 6.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 167.4, 148.9, 133.5, 132.7, 129.2, 127.6, 127.4, 125.9, 122.5, 120.9, 119.8 ppm; IR (KBr): 3408, 2922, 2851, 1649, 1613, 1576, 1543, 1489, 1452, 1367, 1314, 1022, 748, 703, 620 cm^{-1}; LRMS (ESI): m/z $[M-H]^-$ calcd for $C_{13}H_{10}NO_2$ 212.0717, found 212.1760.

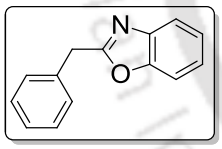
4.6. Characterization data

2-Phenylbenzo[*d*]oxazole[126b] (entry 1, Table 4.1.2)



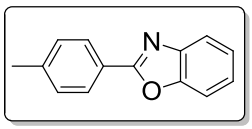
Yield: 184 mg (92%); white solid; R_f = 0.50 (EtOAc:Hexane, 0.5:9.5); mp: 102-103 °C (lit. 102 ºC); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.24-8.22 (m, 2H), 7.78-7.76 (m, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.47-7.45 (m, 2H), 7.32-7.29 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.9, 150.7, 142.1, 131.4, 128.8, 127.6, 127.1, 125.1, 124.5, 120.0, 110.5 ppm; IR (KBr): 3060, 2922, 1616, 1551, 1447, 1241, 1052, 924, 745, 686 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{13}H_{10}NO$ 196.0757, found 196.0754; Anal. Calcd for $C_{13}H_9NO$: C, 79.98; H, 4.65; N, 7.17; found: C, 80.08; H, 4.59; N, 7.12.

2-Benzylbenzo[*d*]oxazole[127] (entry 2, Table 4.1.2)



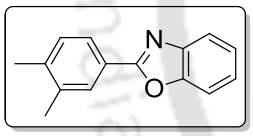
Yield: 192 mg (92%); yellow oil; R_f = 0.50 (EtOAc:Hexane, 1.0:9.0); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69-7.67 (m, 1H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.46-7.44 (m, 1H), 7.38-7.37 (m, 2H), 7.35-7.32 (m, 2H), 7.29-7.27 (m, 1H), 4.26 ppm (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.4, 151.2, 141.5, 134.9, 129.2, 129.0, 127.5, 124.9, 124.3, 120.0, 110.0, 35.4 ppm; IR (KBr) 2923, 2852, 1614, 1548, 1483, 1452, 1400, 1244, 754, 829, 455 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_{12}NO$ 210.0914, found 210.0917; Anal. Calcd for $C_{14}H_{11}NO$: C, 80.36; H, 5.30; N, 6.69; found: C, 80.32; H, 5.26; N, 6.72.

2-(*p*-Tolyl)benzo[*d*]oxazole[126b] (entry 3, Table 4.1.2)



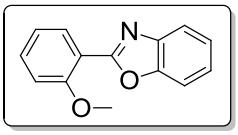
Yield: 186 mg (89%); colourless solid; R_f = 0.50 (EtOAc:Hexane, 1.0:9.0); mp: 114-115 °C (lit. 115-116 ºC); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.14 (d, *J* = 8.0 Hz, 2H), 7.77-7.75 (m, 1H), 7.57-7.56 (m, 1H), 7.34-7.32 (m, 4H), 2.44 ppm (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 163.5, 150.9, 142.3, 142.2, 129.8, 127.8, 125.0, 124.7, 124.6, 120.0, 110.7, 21.8 ppm; IR (KBr): 2929, 2842, 1612, 1541, 1484, 1451, 1420, 1245, 751, 819, 443 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_{12}NO$ 210.0914, found 210.0912; Anal. Calcd for $C_{14}H_{11}NO$: C, 80.36; H, 5.30; N, 6.69; found: C, 80.44; H, 5.29; N, 6.64.

2-(3,4-Dimethylphenyl)benzo[*d*]oxazole[128] (entry 4, Table 4.1.2)



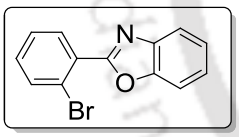
Yield: 196 mg (88%); colorless solid; R_f = 0.50 (EtOAc:Hexane, 1.0:9.0); mp: 112-113 °C (lit. 113-115 ºC); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.03 (s, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.75-7.74 (m, 1H), 7.55-7.54 (m, 1H), 7.34-7.30 (m, 2H), 6.23 (d, *J* = 8.0 Hz, 1H), 2.34 (s, 3H), 2.32 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.6, 150.8, 142.3, 141.0, 137.5, 130.4, 128.9, 125.3, 125.0, 124.8, 124.3, 119.9, 110.6, 20.2, 19.9 ppm; IR (KBr): 2942, 1618, 1554, 1438, 1242, 1054, 926, 741, 683, 452 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{15}H_{14}NO$ 224.1070, found 224.1067; Anal. Calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27; found: C, 80.71; H, 5.84; N, 6.31.

2-(2-Methoxyphenyl)benzo[*d*]oxazole[129] (entry 5, Table 4.1.2)



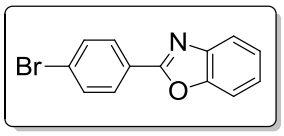
Yield: 183 mg (81%); yellow solid; R_f = 0.40 (EtOAc:Hexane, 1.0:9.0); mp: 52-54 °C (lit. 53-54 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (d, *J* = 8.0 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.60-7.58 (m, 1H), 7.52-7.48 (m, 1H), 7.36-7.34 (m, 2H), 7.26-7.09 (m, 2H), 4.03 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.8, 158.7, 150.5, 142.3, 139.5, 133.0, 131.5, 125.1, 124.5, 120.9, 120.4, 112.3, 110.6, 56.4 ppm; IR (KBr): 3063, 2920, 1615, 1550, 1448, 1345, 1284, 1239, 1145, 1055, 755, 412 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_{12}NO_2$ 226.0863, found 226.0860; Anal. Calcd for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22; found: C, 74.73; H, 4.91; N, 6.17.

2-(2-Bromophenyl)benzo[*d*]oxazole[129] (entry 6, Table 4.1.2)



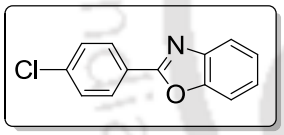
Yield: 244 mg (90%); colorless solid; R_f = 0.50 (EtOAc:Hexane, 1.0:9.0); mp: 53-54 °C (lit. 54-55 °C); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.07 (d, *J* = 8.0 Hz, 1H), 7.86-7.85 (m, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.63-7.61 (m, 1H), 7.48-7.45 (m, 1H), 7.40-7.36 ppm (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 161.7, 150.8, 141.8, 134.9, 132.4, 132.2, 128.6, 127.7, 125.8, 124.9, 122.1, 120.8, 111.0 ppm; IR (KBr): 3061, 2923, 1612, 1614, 1532, 1444, 1343, 1281, 1235, 1190, 1105, 1001, 766, 452 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{13}H_9BrNO$ 273.9863, found 273.9861; Anal. Calcd for $C_{13}H_8BrNO$: C, 56.96; H, 2.94; N, 5.11; found: C, 56.91; H, 2.98; N, 5.16.

2-(4-Bromophenyl)benzo[*d*]oxazole[126b] (entry 7, Table 4.1.2)



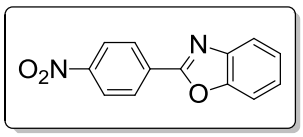
Yield: 231 mg (85%); white solid; R_f = 0.50 (EtOAc:Hexane, 1.0:9.0); mp: 156-157 °C (lit. 156-158 ºC); 1H NMR (400 MHz, $CDCl_3$): δ = 8.08 (d, *J* = 8.0 Hz, 2H), 7.76-7.73 (m, 1H), 7.62 (d, *J* = 8.0 Hz, 2H), 7.56-7.54 (m, 1H), 7.35-6.33 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.3, 150.9, 142.1, 132.3, 129.1, 126.3, 126.2, 125.5, 124.9, 120.2, 110.8 ppm; IR (KBr): 3024, 2921, 1614, 1548, 1483, 1452, 1401, 1244, 1009, 829, 740, 494 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{13}H_9BrNO$ 273.9863, found 273.9865; Anal. Calcd for $C_{13}H_8BrNO$: C, 56.96; H, 2.94; N, 5.11. found: C, 56.98; H, 2.93; N, 5.08.

2-(4-Chlorophenyl)benzo[*d*]oxazole[126b] (entry 8, Table 4.1.2)



Yield: 199 mg (87%); white solid; R_f = 0.50 (EtOAc:Hexane, 1.5:8.5); mp: 152-154 °C (lit. 153-154 ºC); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (d, *J* = 8.0 Hz, 2H), 7.76-7.74 (m, 1H), 7.58-7.55 (m, 1H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.37-7.34 ppm (m, 2H);^{13}C NMR (100 MHz, $CDCl_3$): δ 162.1, 150.8, 142.0, 137.8, 129.3, 128.9, 125.9, 125.4, 124.8, 120.0, 110.6 ppm; IR (KBr): 3021, 2923, 2811, 1616, 1483, 1452, 832, 738, 532, 455 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{13}H_9ClNO$ 230.0368, found 230.0366; Anal. Calcd for $C_{13}H_8ClNO$: C, 67.99; H, 3.51; N, 6.10; found: C, 68.04; H, 3.49; N, 6.04.

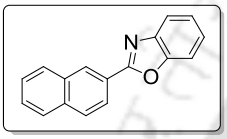
2-(4-Nitrophenyl)benzo[*d*]oxazole[130] (entry 9, Table 4.1.2)



Yield: 214 mg (89%); yellowish solid; R_f = 0.50 (EtOAc:Hexane, 1.0:9.0); mp: 266-268 °C (lit. 266-268 ºC); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.58 (d, *J* = 7.6 Hz, 1H), 8.39-8.36 (m, 2H), 7.84 (d, *J* =

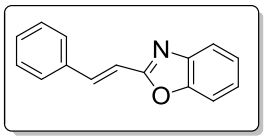
7.6 Hz, 1H), 7.82 (t, *J* = 6.0 Hz, 2H), 7.74-7.71 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.8, 151.1, 148.9, 142.0, 135.5, 133.2, 130.4, 126.3, 122.7, 120.7, 111.1 ppm; IR (KBr): 3023, 2920, 2821, 1611, 1484, 1453, 831, 737 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{13}H_9N_2O_3$ 241.0608, found 241.0610; Anal. Calcd for $C_{13}H_8N_2O_3$: C, 65.00; H, 3.36; N, 11.66; found: C, 65.04; H, 3.40; N, 11.64.

2-(Naphthalen-2-yl)benzo[*d*]oxazole[128] (entry 10, Table 4.1.2)



Yield: 220 mg (90%); white solid; R_f = 0.50 (EtOAc:Hexane, 1.0:9.0); mp: 115-116°C (lit. 116-118 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.75 (s, 1H), 8.27 (d, *J* = 8.0 Hz, 1H), 7.95-7.88 (m, 2H), 7.80 (d, *J* = 8.0 Hz, 2H), 7.59-7.54 (m, 3H), 7.33 ppm (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.4, 151.1, 142.4, 134.9, 133.2, 129.1, 129.0, 128.3, 128.1, 127.9, 125.3, 124.8, 124.5, 124.1, 120.2, 110.7 ppm; IR (KBr): 3025, 2942, 2842, 1624, 1481, 1455, 823, 756, 532, 445 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{17}H_{12}NO$ 246.0914, found 246.0912; Anal. Calcd for $C_{17}H_{11}NO$: C, 83.25; H, 4.52; N, 5.71; found: C, 83.27; H, 4.50; N, 5.73.

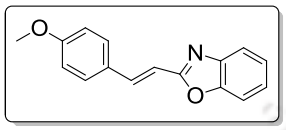
(*E*)-2-Styrylbenzo[*d*]oxazole[130] (entry 11, Table 4.1.2)



Yield: 201 mg (91%);Yellow solid; R_f = 0.50 (EtOAc:Hexane, 1.0:9.0); mp: 85-87 °C (lit. 85-86 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 8.0 Hz, 1H), 7.72-7.70 (m, 1H), 7.60-7.53 (m, 2H), 7.52-7.51 (m, 1H), 7.43-7.37 (m, 2H), 7.34-7.31 (m, 2H), 7.06 ppm (d, *J* = 16.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.0, 150.6, 142.3, 139.7, 135.3, 130.0, 129.2, 127.7, 125.4, 124.7, 120.0, 114.8, 110.5 ppm; IR (KBr): 3026, 2924, 2852, 1641, 1532, 1452, 1259, 1240, 1176, 967, 837, 761, 742, 495 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$

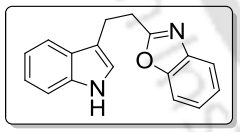
calcd for $C_{15}H_{12}NO$ 222.0914, found 222.0911; Anal. Calcd for $C_{15}H_{11}NO$: C, 81.43; H, 5.01; N, 6.33; found: C, 81.45; H, 4.99; N, 6.30.

(*E*)-2-(4-Methoxystyryl)benzo[*d*]oxazole (entry 12, Table 4.1.2)



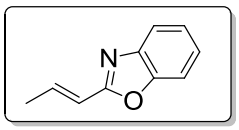
Yield: 218 mg (87%); yellowish solid; R_f = 0.50 (EtOAc:Hexane, 1.0:9.0); mp: 126-129 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68 (d, *J* = 8.0 Hz, 2H), 7.53-7.48 (m, 3H), 7.30-7.27 (m, 2H), 6.92-6.89 (m, 3H), 3.82 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.4, 161.1, 150.5, 142.4, 139.3, 129.3, 128.0, 125.1, 124.5, 119.8, 114.4, 111.6, 110.5, 55.6 ppm; IR (KBr): 3021, 2932, 2811, 1612, 1487, 1451, 833, 713, 532, 456 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{16}H_{14}NO_2$ 252.1020, found 252.1021; Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57; found: C, 76.49; H, 5.24; N, 5.59.

2-[2-(1-*H*-indol-3-yl)ethyl]benzo[*d*]oxazole (entry 13, Table 4.1.2)



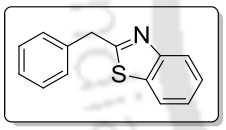
Yield: 228 mg (87%); yellow solid; R_f = 0.50 (EtOAc:Hexane, 1.0:9.0); mp: 114-117 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.63 (s, 1H), 8.47 (d, *J* = 8.0 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.69-7.67 (m, 2H), 7.49-7.42 (m, 2H), 7.38-7.30 (m, 2H), 4.15 (t, *J* = 6.0 Hz, 2H), 1.27 ppm (t, *J* = 6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.2, 150.9, 141.1, 136.4, 127.2, 124.8, 124.4, 122.2, 121.7, 120.6, 119.5, 118.6, 114.4, 111.4, 110.6, 29.6, 22.7 ppm; IR (KBr): 3302, 3021, 2922, 2862, 1643, 1531, 1454, 1257, 1172, 968, 847, 762, 752, 492 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{17}H_{15}N_2O$ 263.1179, found 263.1177; Anal. Calcd for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; N, 10.68; found: C, 77.81; H, 5.39; N, 10.66.

(*E*)-2-(Prop-1-en-1-yl)benzo[*d*]oxazole (entry 14, Table 4.1.2)



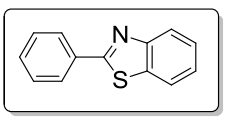
Yield: 135 mg (85%); yellowish oil; R_f = 0.50 (EtOAc:Hexane, 1.0:9.0); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67-7.66 (m, 1H), 7.47-7.45 (m, 1H), 7.29-7.27 (m, 2H), 7.04-7.00 (m, 1H), 6.46-6.43 (m, 1H), 1.99 ppm (d, *J* = 4.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.6, 150.4, 142.0, 139.3, 125.0, 124.4, 119.9, 118.4, 110.4, 18.9 ppm; IR (KBr): , 3021, 2852, 1651, 1531, 1451, 1250, 1242, 1172, 957, 834, 754, 741, 532, 493 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{10}H_{10}NO$ 160.0757, found 160.0762; Anal. Calcd for $C_{10}H_9NO$: C, 75.45; H, 5.70; N, 8.80; found: C, 75.42; H, 5.71; N, 8.78.

2-Benzylbenzo[*d*]thiazole[131] (entry 1, Table 4.1.3)



Yield: 207 mg (92%); oil; R_f = 0.50 (EtOAc:Hexane, 1.0:9.0); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (d, *J* = 8.0 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.57-7.50 (m, 2H), 7.34-7.27 (m, 5H), 3.61 ppm (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.8, 154.1, 134.4, 131.2, 129.4, 129.2, 128.7, 127.8, 126.5, 123.4, 122.4, 41.6 ppm; IR (KBr): 2925, 2852, 1612, 1431, 1222, 1183, 1071, 812, 551 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_{12}NS$ 226.0685, found 226.0690; Anal. Calcd for $C_{14}H_{11}NS$: C, 74.63; H, 4.92; N, 6.22; S, 14.23; found: C, 74.70; H, 4.90; N, 6.20; S, 14.20.

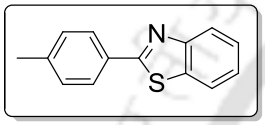
2-Phenylbenzo[*d*]thiazole[74] (entry 2, Table 4.1.3)



Yield: 189 mg (90%); coloress solid; R_f = 0.50 (EtOAc:Hexane, 1.0:9.0); mp: 111-112 °C (lit. 110-111 ºC); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.12 (d, *J* = 8.0 Hz, 1H), 8.10-8.08 (m, 3H), 7.52-7.48 ppm (m, 5H); ^{13}C

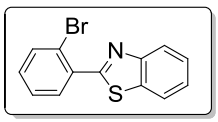
NMR (100 MHz, $CDCl_3$): δ = 168.3, 154.4, 133.9, 131.6, 129.3, 128.0, 127.8, 126.5, 125.4, 123.5, 121.8, 120.4 ppm; IR (KBr): 3076, 2923, 1587, 1545, 1479, 1438, 1306, 1224, 1104, 732, 523 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{13}H_{10}NS$ 212.0529, found 212.0525; Anal. Calcd for $C_{13}H_9NS$: C, 73.90; H, 4.29; N, 6.63; S, 15.18; found: C, 73.99; H, 4.27; N, 6.59; S, 15.15.

2-(*p*-Tolyl)benzo[*d*]thiazole[132] (entry 3, Table 4.1.3)



Yield: 200 mg (89%); colorless solid; R_f = 0.50 (EtOAc:Hexane, 1.0:9.0); mp: 78-81 °C (lit. 80-82 ºC); ^1H NMR (400 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 8.0 Hz, 1H), 7.95 (d, *J* = 8.0 Hz, 2H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.46 (t, *J* = 8.0 Hz, 1H), 7.35 (t, *J* = 8.0 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 2H), 2.41 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.5, 154.4, 141.6, 135.2, 129.9, 127.7, 126.5, 125.2, 124.3, 123.3, 122.3, 121.8, 21.5 ppm; IR (KBr): 2924, 2853, 1610, 1434, 1260, 1181, 1077, 817, 552 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_{12}NS$ 226.0685, found 226.0689; Anal. Calcd for $C_{14}H_{11}NS$: C, 74.63; H, 4.92; N, 6.22; S, 14.23; found: C, 74.70; H, 4.94; N, 6.20; S, 14.20.

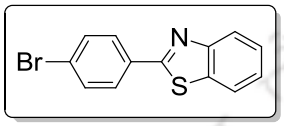
2-(2-Bromophenyl)benzo[*d*]thiazole[133] (entry 4, Table 4.1.3)



Yield: 253 mg (88%); white solid; R_f = 0.50 (EtOAc:Hexane, 1.0:9.0); mp: 64-66 °C (lit. 63.3-65.1 ºC); ^1H NMR (600 MHz, $CDCl_3$): δ = 8.07 (d, *J* = 7.6 Hz, 1H), 8.00-7.96 (m, 2H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.68-7.66 (m, 1H), 7.64-7.62 (d, *J* = 7.6 Hz, 1H), 7.52 (t, *J* = 8.0 Hz, 1H), 7.41 ppm (t, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.4, 154.2, 136.0, 134.0, 132.7, 130.5, 130.1, 128.4, 126.8, 126.4, 125.8, 123.7, 121.9 ppm; IR (KBr): 3072, 2922, 1577, 1542,

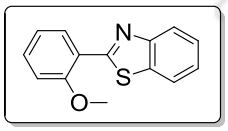
1480, 1437, 1302, 1245, 1221, 1101, 1076, 1053, 766, 532, cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{13}H_9BrNS$ 289.9634, found 289.9632; Anal. Calcd for $C_{13}H_8BrNS$: C, 53.81; H, 2.78; N, 4.83; S, 11.05; found: C, 53.85; H, 2.75; N, 4.82; S, 11.08.

2-(4-Bromophenyl)benzo[*d*]thiazole[133] (entry 5, Table 4.1.3)



Yield: 256 mg (89%); white solid; R_f = 0.50 (EtOAc:Hexane, 1.0:9.0); mp: 129-130 °C (lit. 128.7-129.9 ºC); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (d, *J* = 7.6 Hz, 3H), 7.95 (d, *J* = 8.0 Hz, 2H), 7.89 (t, *J* = 8.0 Hz, 2H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.56 ppm (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.0, 154.3, 132.5, 131.9, 127.1, 126.9, 125.7, 124.3, 123.5, 122.3, 121.9 ppm; IR (KBr): 2922, 2830, 1638, 1449, 1311, 1268, 1172, 1021, 761, 727, 531 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{13}H_9BrNS$ 289.9634, found 289.9632; Anal. Calcd for $C_{13}H_8BrNS$: C, 53.81; H, 2.78; N, 4.83; S, 11.05; found: C, 53.85; H, 2.75; N, 4.84; S, 11.06.

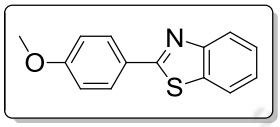
2-(2-Methoxyphenyl)benzo[*d*]thiazole[134] (entry 6, Table 4.1.3)



Yield: 219 mg (91%); white solid; R_f = 0.50 (EtOAc:Hexane, 1.0:9.0); mp: 102-104°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.52 (d, *J* = 8.0 Hz, 1H), 8.08 (d, *J* = 8.0 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.50-7.44 (m, 2H), 7.35 (t, *J* = 8.0 Hz, 1H), 7.15-7.06 (m, 2H), 4.06 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.4, 157.5, 152.4, 136.3, 132.0, 129.8, 126.1, 124.8, 123.0, 121.4, 111.9, 55.9 ppm; IR (KBr): 2916, 2843, 1598, 1497, 1460, 1309, 1248, 1115, 1016, 757, 728, 552 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_{12}NOS$ 242.0635, found 242.0638; Anal. Calcd

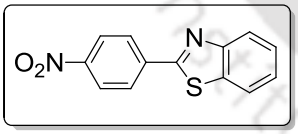
for $C_{14}H_{11}NOS$: C, 69.68; H, 4.59; N, 5.80; S, 13.29; found: C, 69.70; H, 4.58; N, 5.81; S, 13.30.

2-(4-Methoxyphenyl)benzo[*d*]thiazole[74] (entry 7, Table 4.1.3)



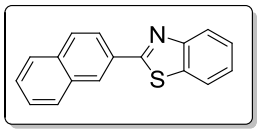
Yield: 216 mg (90%); white solid; R_f = 0.50 (EtOAc:Hexane, 1.0:9.0); mp: 118-119 °C (lit. 119-120 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 8.4 Hz, 3H), 8.84 (d, *J* = 8.0 Hz, 1H), 7.44 (t, *J* = 8.0 Hz, 1H), 7.32 (t, *J* = 8.0, Hz, 1H), 6.96 (d, *J* = 8.0 Hz, 2H), 3.82 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.0, 162.2, 154.4, 135.1, 131.7, 129.3, 126.4, 125.0, 123.0, 121.7, 114.6, 55.7 ppm; IR (KBr): 2936, 1601, 1558, 1465, 1430, 1329, 1279, 1160, 1139, 1076, 969, 531 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_{12}NOS$ 242.0635, found 242.0636; Anal. Calcd for $C_{14}H_{11}NOS$: C, 69.68; H, 4.59; N, 5.80; S, 13.29; found: C, 69.70; H, 4.58; N, 5.81; S, 13.30.

2-(4-Nitrophenyl) benzo[*d*]thiazole[130] (entry 8, Table 4.1.3)



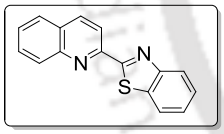
Yield: 207 mg (81%); yellow solid; R_f = 0.50 (EtOAc:Hexane, 1.5:8.5); mp: 227-228 °C (lit. 228-229 °C); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.33 (d, *J* = 8.0 Hz, 2H), 8.26 (d, *J* = 8.0 Hz, 2H), 8.25-8.22 (m, 1H), 8.21-8.11 (m, 1H), 7.55 (t, *J* = 6.0 Hz, 1H), 7.46 ppm (t, *J* = 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.9, 154.3, 150.7, 149.3, 139.4, 136.1, 130.9, 128.4, 127.0, 124.5, 123.7, 122.0 ppm; IR (KBr): 2923, 1642, 1553, 1452, 1322, 1289, 1161, 1129, 1072, 962, 542, 514 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{13}H_9N_2O_2S$ 257.0380, found 257.0378; Anal. Calcd for $C_{13}H_8N_2O_2S$: C, 60.93; H, 3.15; N, 10.93; S, 12.51; found: C, 60.90; H, 3.18; N, 10.90; S, 12.49.

2-(Naphthalen-2-yl)benzo[*d*]thiazole[135] (entry 9, Table 4.1.3)



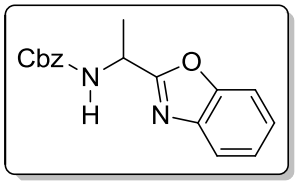
Yield: 229 mg (88%); white solid; R_f = 0.50 (EtOAc:Hexane, 1.0:9.0); mp: 126-127 °C (lit. 125-127 ºC); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.60 (s, 1H), 8.21 (d, *J* = 8.0 Hz, 1H), 8.06 (d, *J* = 7.8 Hz, 1H), 7.98-7.93 (m, 3H), 7.89-7.87 (m, 2H), 7.60-7.50 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.0, 154.5, 135.7, 134.9, 132.8, 131.2, 129.6, 129.1, 128.4, 128.0, 127.7, 126.8, 125.5, 124.7, 123.5, 121.8, 120.4 ppm; IR (KBr): 2922, 2832, 1634, 1466, 1311, 1252, 1262, 1177, 1022, 761, 725, 534, 527; cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{17}H_{12}NS$ 262.0685, found 262.0686; Anal. Calcd for $C_{17}H_{11}NS$: C, 78.13; H, 4.24; N, 5.36; S, 12.27; found: C, 78.18; H, 4.22; N, 5.35; S, 12.25.

2-(Quinolin-3-yl)benzo[*d*]thiazole (entry 10, Table 4.1.3)



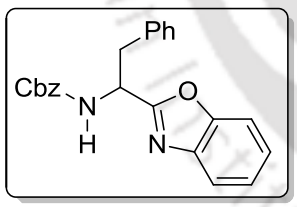
Yield: 222 mg (85%); yellowish solid; R_f = 0.50 (EtOAc:Hexane, 1.0:9.0); mp: 175-179 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.46 (d, *J* = 8.0 Hz, 2H), 8.27 (d, *J* = 8.0 Hz, 1H), 8.17 (d, *J* = 8.0 Hz, 1H), 8.11 (d, *J* = 8.0 Hz, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.75 (t, *J* = 8.0 Hz, 1H), 7.57 (t, *J* = 8.0 Hz, 1H), 7.51 (t, *J* = 8.0 Hz, 1H), 7.42 ppm (t, *J* = 8.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.1, 154.6, 151.5, 148.1, 137.2, 137.0, 130.3, 130.0, 129.2, 127.9, 127.8, 126.5, 126.1, 124.0, 122.2, 118.6 ppm; IR (KBr): 2923, 2852, 1617, 1494, 1500, 1325, 1260, 1118, 995, 753, 727, 628 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{16}H_{11}N_2S$ 263.0638, found 263.0639; Anal. Calcd for $C_{16}H_{10}N_2S$: C, 73.26; H, 3.84; N, 10.68; S, 12.22; found: C, 73.30; H, 3.82; N, 10.65; S, 12.21.

Benzyl (1-(benzo[*d*]oxazol-2-yl)ethyl)carbamate (entry 1, Table 4.1.4)



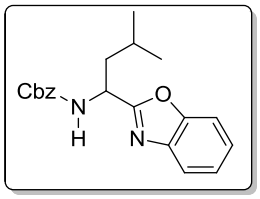
Yield: 207 mg (70%); white solid; R_f = 0.50 (EtOAc:Hexane, 3.0:7.0); mp: 83-85 °C; $[\alpha]_D^{25}$ = + 6.2 ($CHCl_3$, c = 0.33); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.68 (d, *J* = 8.4 Hz, 1H), 7.50 (d, *J* = 6.0 Hz, 1H), 7.36-7.34 (m, 4H), 7.33-7.29 (m, 3H), 5.60 (br, NH), 5.19 (d, *J* = 8.2 Hz, 1H), 5.18 (s, 2H), 1.66 ppm (d, *J* = 6.0 Hz, 3H);^{13}C NMR (150 MHz, $CDCl_3$): δ 166.7, 155.8, 151.1, 140.9, 136.4, 128.7, 128.4, 127.2, 125.4, 124.7, 120.2, 111.0, 67.4, 45.9, 29.9, 20.3 ppm; IR (KBr): 3334, 3032, 2938, 1693, 1608, 1531, 1456, 1247, 1048, 755, 691 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{17}H_{17}N_2O_3$ 297.1234, found 297.1243; Anal. Calcd for $C_{17}H_{16}N_2O_3$: C, 68.91; H, 5.44; N, 9.45; found: C, 68.94; H, 5.42; N, 9.42.

Benzyl (1-(benzo[*d*]oxazol-2-yl)-2-phenylethyl)carbamate (entry 2, Table 4.1.4)



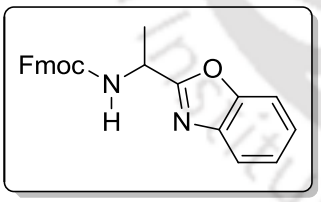
Yield: 267 mg (72%); white powder; R_f = 0.50 (EtOAc:Hexane, 2.5:7.5); mp: 87-90 °C; $[\alpha]_D^{25}$ = + 13.6 ($CHCl_3$, c = 1.0); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.67 (d, *J* = 6.0 Hz, 1H), 7.50 (d, *J* = 6.0 Hz, 1H), 7.34-7.32 (m, 7H), 7.23-7.19 (m, 3H), 7.05-7.01 (m, 2H), 5.64 (br, NH), 5.45-5.41(q, *J* = 6.0 Hz, 2H), 5.12 (s, 2H), 3.30 ppm (dd, *J* = 6.0, 6.0 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 165.4, 155.9, 150.9, 140.8, 136.4, 135.6, 129.5, 128.8, 128.7, 128.4, 128.3, 127.3, 125.4, 124.8, 120.3, 110.9, 67.3, 55.0, 40.0 ppm; IR (KBr): 3339, 3033, 2936, 1697, 1609, 1534, 1458, 1257, 1081, 970, 755, 698 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{23}H_{21}N_2O_3$ 373.1547, found 373.1551; Anal. Calcd for $C_{23}H_{20}N_2O_3$: C, 74.18; H, 5.41; N, 7.52; found: 74.16; H, 5.46; N, 7.54.

Benzyl (1-(benzo[*d*]oxazol-2-yl)-3-methylbutyl)carbamate (entry 3, Table 4.1.4)



Yield: 226 mg (67%); amorphous solid; R_f = 0.40 (EtOAc:Hexane, 2.0:8.0); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.70-7.69 (d, *J* = 6.0 Hz, 1H), 7.50 (d, *J* = 6.0 Hz, 1H), 7.36-7.32 (m, 7H), 5.49 (br, NH), 5.19 (t, *J* = 6.0 Hz, 1H), 5.10 (s, 2H), 1.89 (t, *J* = 8.0 Hz, 1H), 1.81 (t, *J* = 7.6 Hz, 1H), 1.72-1.68 (m, 1H), 0.98 ppm (d, *J* = 6.0 Hz, 6 H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 166.7, 156.0 150.8, 141.0, 136.3, 128.7, 128.4, 128.3, 125.3, 124.6, 120.2, 110.9, 67.3, 48.5, 43.5, 24.9, 22.9, 22.2 ppm; IR (KBr): 3298, 2889, 1700, 1528, 1260, 1055, 741, 702 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{20}H_{23}N_2O_3$ 339.1704, found 339.1706, Anal. Calcd for $C_{20}H_{22}N_2O_3$: C, 70.99; H, 6.55; N, 8.28; found: C, 71.01; H, 6.52; N, 8.26.

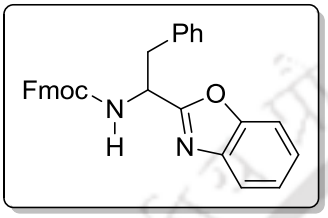
(9*H*-Fluoren-9-yl)methyl (1-(benzo[*d*]oxazol-2-yl)ethyl)carbamate (entry 4, Table 4.1.4)



Yield: 257 mg (67%); white solid; R_f = 0.40 (EtOAc:Hexane, 2.0:8.0); mp: 152-155 °C; $[\alpha]_D^{25}$ = + 2.6 ($CHCl_3$, c = 0.93); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.76 (d, *J* = 6.0 Hz, 1H), 7.71 (t, *J* = 6.0 Hz, 1H), 7.62 (t, *J* = 7.8 Hz, 2H), 7.52 (t, *J* = 6.0 Hz, 1H), 7.35-7.33 (m, 2H), 7.32-7.30 (m, 4H), 5.74 (br, NH), 5.22 (t, *J* = 6.0 Hz, 1H), 4.45 (d, *J* = 6.0 Hz, 2H), 4.24 (t, *J* = 6.0 Hz, 1H), 1.68 ppm (d, *J* = 6.0 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 166.7, 155.9, 151.0, 144.1, 143.9, 141.5, 140.9, 127.9, 127.2, 125.4, 125.3, 124.7, 120.2, 110.9, 67.3, 47.3, 45.9, 20.3 ppm; IR (KBr): 3321, 2932, 1690, 1542, 1452, 1251, 1080, 744, 686 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{24}H_{21}N_2O_3$ 385.1547, found 385.1557,

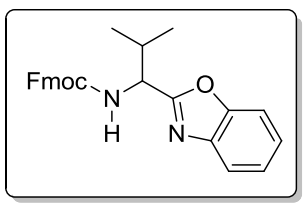
Anal. Calcd for $C_{24}H_{20}N_2O_3$: C, 74.98; H, 5.24; N, 7.29; found: C, 74.95; H, 5.30; N, 7.29.

(9*H*-Fluoren-9-yl)methyl (1-(benzo[*d*]oxazol-2-yl)-2-phenylethyl)carbamate (entry 5, Table 4.1.4)



Yield: 326 mg (71%); white crystalline solid; R_f = 0.50 (EtOAc:Hexane, 2.0:8.0); mp: 86-88 °C; $[\alpha]_D^{25}$ = – 1.2 ($CHCl_3$, c = 0.69); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.76 (d, *J* = 6.0 Hz, 2H), 7.69 (d, *J* = 6.0 Hz, 1H), 7.59-7.55 (m, 2H), 7.52 (d, *J* = 6.0 Hz, 1H), 7.39-7.36 (m, 2H), 7.36-7.34 (m, 2H), 7.30-7.28 (m, 2H), 7.23-7.21 (m, 3H), 7.05 (br, 2H), 5.52 (br, NH), 5.44 (t, *J* = 6.0 Hz, 1H), 4.46 (d, *J* = 6.0 Hz, 2H), 4.36 (t, *J* = 6.0 Hz, 1H), 3.33 ppm (dd, *J* = 6.0, 6.0 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 165.3, 155.8, 150.9, 144.0, 143.9, 141.5, 140.9, 135.7, 129.6, 128.8, 127.9, 127.4, 127.3, 125.4, 125.3, 124.8, 120.3, 120.1, 111.0, 67.3, 51.1, 47.4, 40.0 ppm; IR (KBr): 3324, 3070, 2963, 1690, 1623, 1550, 1280, 1037, 745 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{30}H_{25}N_2O_3$ 461.1865, found 461.1867; Anal. Calcd for $C_{30}H_{24}N_2O_3$: C, 78.24; H, 5.25; N, 6.08; found: C, 78.30; H, 5.28; N, 6.05.

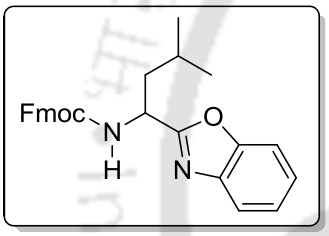
(9*H*-Fluoren-9-yl)methyl (1-(benzo[*d*]oxazol-2-yl)-2-methylpropyl) carbamate (entry 6, Table 4.1.4)



Yield: 264 mg (64%); yellowish solid; R_f = 0.40 (EtOAc:Hexane, 2.0:8.0); mp: 85-86 °C; $[\alpha]_D^{25}$ = – 2.3 ($CHCl_3$, c = 0.61); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.76 (d, *J* = 6.0 Hz, 2H), 7.72 (t, *J* = 6.0 Hz, 1H), 7.61 (t, *J* = 8.4 Hz, 2H), 7.53-7.52 (m, 1H), 7.39-7.28 (m, 6H), 5.71 (br, NH), 5.02 (t, *J* = 6.0 Hz, 1H), 4.46 (d, *J* = 6.0 Hz, 2H), 4.25 (t, *J* =

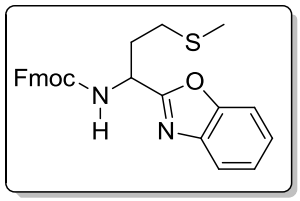
6.0 Hz, 1H), 2.39-2.35 (m, 1H), 1.01 ppm (d, *J* = 6.0 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 165.8, 156.4, 150.9, 144.1, 143.9, 141.5, 140.9, 127.9, 127.2, 125.3, 124.7, 120.2, 110.9, 67.3, 55.5, 47.4, 32.9, 19.1, 18.2 ppm; IR (KBr): 3314, 2961, 1695, 1611, 1432, 1239, 1027, 739 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{26}H_{25}N_2O_3$ 413.1860, found 413.1864; Anal. Calcd for $C_{26}H_{24}N_2O_3$: C, 75.71; H, 5.86; N, 6.79; found: C, 75.75; H, 5.89; N, 6.76.

(9*H*-Fluoren-9-yl)methyl (1-(benzo[*d*]oxazol-2-yl)-3-methylbutyl) carbamate (entry 7, Table 4.1.4)



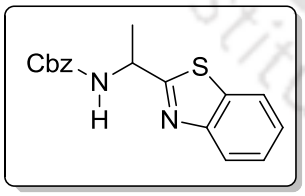
Yield: 277 mg (65%); white solid; R_f = 0.50 (EtOAc:Hexane, 3.0:7.0); mp: 80-82 °C; $[\alpha]_D^{25}$ = + 4.0 ($CHCl_3$, c = 0.40); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.75 (d, *J* = 6.0 Hz, 2H), 7.71 (t, *J* = 6.0 Hz, 1H), 7.61 (t, *J* = 8.0 Hz, 2H), 7.51 (d, *J* = 6.0 Hz, 1H), 7.39-7.34 (m, 4H), 7.29 (t, *J* = 6.0 Hz, 2H), 5.54 (br, NH), 5.19 (t, *J* = 6.0 Hz, 1H), 4.44 (d, *J* = 6.0 Hz, 2H), 4.21 (t, *J* = 6.0 Hz, 1H), 1.89 (d, *J* = 6.0 Hz, 1H), 1.83 (d, *J* = 6.0 Hz, 1H), 1.75-1.71 (m, 1H), 0.99 ppm (d, *J* = 6.0 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 166.7, 156.1, 150.9, 144.1, 143.9, 141.5, 141.0, 127.9, 127.2, 125.3, 124.7, 120.2, 111.0, 67.2, 48.5, 47.4, 43.5, 24.9, 22.9, 22.2 ppm; IR (KBr): 3322, 3064, 2972, 1689, 1539, 1348, 1242, 1030, 761, 672 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{27}H_{27}N_2O_3$ 427.2017, found 427.2015; Anal. Calcd for $C_{27}H_{26}N_2O_3$: C, 76.03; H, 6.14; N, 6.57; found: C, 76.01; H, 6.15; N, 6.60.

(9*H*-Fluoren-9-yl)methyl (1-(benzo[*d*]oxazol-2-yl)-3-(methylthio)propyl) carbamate (entry 8, Table 4.1.4)



Yield: 293 mg (66%); white solid; R_f = 0.40 (EtOAc:Hexane, 3.0:7.0); mp: 94-96 °C; $[\alpha]_D^{25}$ = – 1.6 ($CHCl_3$, c = 1.0); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.76 (d, *J* = 6.0 Hz, 2H), 7.70 (t, *J* = 6.0 Hz, 1H), 7.62 (t, *J* = 8.4 Hz, 2H), 7.52 (d, *J* = 6.0 Hz, 1H), 7.40-7.30 (m, 6H), 5.72 (br, NH), 5.29 (t, *J* = 6.0 Hz, 1H), 4.48 (d, *J* = 7.8 Hz, 2H), 4.24 (t, *J* = 6.0 Hz, 1H), 2.58 (d, *J* = 6.0 Hz, 2H), 2.38 (q, *J* = 6.0 Hz, 1H), 2.21 (q, *J* = 6.0 Hz, 1H), 2.10 ppm (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 165.5, 156.1, 151.0, 143.9, 141.5, 140.9, 127.9, 127.3, 125.5, 125.3, 124.8, 120.3, 111.0, 67.3, 49.4, 47.4, 33.6, 30.0, 15.8 ppm; IR (KBr): 3310, 2923, 1699, 1541, 1452, 1261, 1085, 741, 699 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{26}H_{25}N_2O_3S$ 445.1581, found 445.1586; Anal. Calcd for $C_{26}H_{24}N_2O_3S$: C, 70.25; H, 5.44; N, 6.30; S, 7.21; found: C, 70.28; H, 5.49; N, 6.32; S, 7.20.

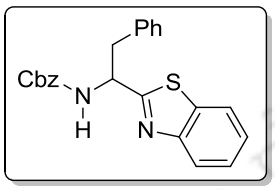
Benzyl (1-(benzo[*d*]thiazol-2-yl)ethyl)carbamate (entry 9, Table 4.1.4)



Yield: 190 mg (61%); white solid; R_f = 0.40 (EtOAc:Hexane, 2.0:8.0); mp: 94-96 °C; $[\alpha]_D^{25}$ = + 3.7 ($CHCl_3$, c = 0.43); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, *J* = 8.0 Hz, 1H),.84 (d, *J* = 8.0 Hz, 1H), 7.47 (t, *J* = 8.0 Hz, 1H), 7.39-7.37 (m, 6H), 5.71 (br, NH), 5.29-5.25 (q, *J* = 6.0 Hz, 1H), 5.15 (s, 2H), 1.68 ppm (d, *J* = 8.0 Hz, 3H);^{13}C NMR (150 MHz, $CDCl_3$): δ 173.7, 155.8, 153.3, 136.4, 135.1, 128.7, 128.4, 126.3, 125.3, 123.2, 121.9, 67.3, 50.0, 22.2 ppm; IR (KBr): 3341, 2961, 1696, 1536, 1309, 1246, 1211, 1087, 1011, 934, 764, 691, 647 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{17}H_{17}N_2O_2S$ 313.1006, found

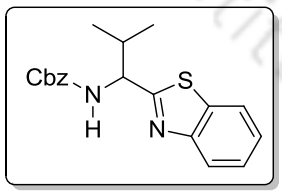
313.1009; Anal. Calcd for $C_{11}H_{17}N_2O_2S$: C, 65.36; H, 5.16; N, 8.97; S, 10.26; found: C, 65.31; H, 5.19; N, 9.00; S, 10.27.

Benzyl (1-(benzo[*d*]oxazol-2-yl)-2-phenylethyl)carbamate (entry 10, Table 4.1.4)



Yield: 264 mg (68%); white solid; R_f = 0.40 (EtOAc:Hexane, 2.0:8.0); mp: 92-94 °C; $[\alpha]_D^{25}$ = + 12.0 ($CHCl_3$, c = 1.0); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.98 (d, *J* = 7.8 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.46 (t, *J* = 8.4 Hz, 1H), 7.37-7.30 (m, 5H), 7.27-7.23 (m, 4H), 7.11 (d, *J* = 6.0 Hz, 2H), 5.74 (br, NH), 5.44 (t, *J* = 6 Hz, 2H), 5.09 (s, 2H), 3.34 ppm (dd, *J* = 6.0, 6.0 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 172.4, 155.9, 153.3, 136.2, 135.0, 129.6, 129.5, 128.7, 128.2, 127.2, 126.3, 125.3, 123.2, 121.9, 67.2, 54.9, 41.6 ppm; IR (KBr): 3325, 2891, 1687, 1522, 1456, 1242, 1050, 743, 709 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{23}H_{21}N_2O_2S$ 389.1319, found 389.1316, Anal. Calcd for $C_{23}H_{20}N_2O_2S$: C, 71.11; H, 5.19; N, 7.21; S, 8.25; found: C, 71.09; H, 5.22; N, 7.28; S, 8.21.

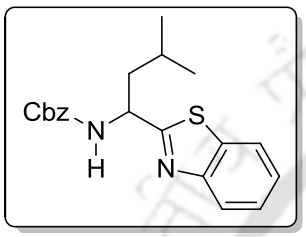
Benzyl (1-(benzo[*d*]thiazol-2-yl)-2-methylpropyl)carbamate (entry 11, Table 4.1.4)



Yield: 214 mg (63%); white solid; R_f = 0.50 (EtOAc:Hexane, 2.5:7.5); mp: 99-100 °C; $[\alpha]_D^{25}$ = + 0.8 ($CHCl_3$, c = 0.52); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.95 (d, *J* = 6.0 Hz, 1H), 7.82 (d, *J* = 6.0 Hz, 1H), 7.44 (t, *J* = 6.0 Hz, 1H), 7.35-7.29 (m, 5H), 7.17-7.15 (m, 1H), 5.70 (br, NH), 5.09 (s, 2H), 5.04 (d, *J* = 6.0 Hz, 1H), 2.44-2.39 (m, 1H), 1.01 (d, *J* = 6.0 Hz, 3H), 0.92 ppm (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 172.2, 156.4, 153.3, 136.4, 134.9, 128.7, 128.4, 128.3, 126.3, 125.2, 123.2, 121.8, 67.4, 59.2, 33.9, 19.6, 17.6 ppm; IR (KBr): 3339, 2960, 1692, 1526, 1305, 1243, 1222, 1084, 1010, 947, 761, 694, 646 cm^-

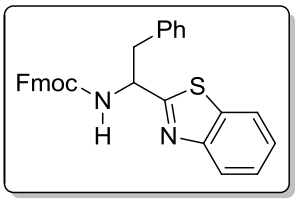
^{1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{19}H_{21}N_2O_2S$ 341.1319, found 341.1320; Anal. Calcd for $C_{19}H_{21}N_2O_2S$: C, 67.03; H, 5.92; N, 8.23; S, 9.42; found: C, 67.09; H, 5.94; N, 8.21; S, 9.38.

Benzyl (1-(benzo[*d*]thiazol-2-yl)-2-methylpropyl)carbamate (entry 12, Table 4.1.4)



Yield: 230 mg (65%); white solid; R_f = 0.40 (EtOAc:Hexane, 2.0:8.0); mp: 88-90 °C; $[\alpha]_D^{25}$ = + 5.3 ($CHCl_3$, c = 0.53); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.98 (d, *J* = 6.0 Hz, 1H), 7.84 (d, *J* = 6.0 Hz, 1H), 7.46 (t, *J* = 6.0 Hz, 1H), 7.37-7.31 (m, 6H), 5.64 (br, NH), 5.26 (t, *J* = 6.0 Hz, 1H), 5.22 (s, 2H), 1.99-1.95 (m, 1H), 1.83-1.78 (m, 2H), 0.98 ppm (d, *J* = 6.0 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 173.7, 156.0, 153.4, 136.4, 134.8, 128.7, 128.3, 128.2, 126.2, 125.2, 123.1, 121.6, 67.3, 52.5, 45.0, 25.0, 23.0, 22.1 ppm; IR (KBr): 3321, 3062, 2962, 1691, 1535, 1318, 1253, 1037, 757, 673 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{20}H_{23}N_2O_2S$ 355.1475, found 355.1478; Anal. Calcd for $C_{20}H_{23}N_2O_2S$: C, 67.77; H, 6.26; N, 7.90; S, 9.05; found: C, 67.71; H, 6.28; N, 7.92; S, 9.01.

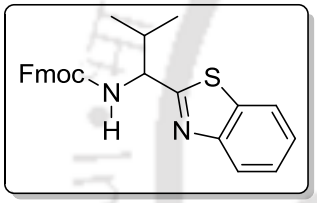
(9*H*-Fluoren-9-yl)methyl (1-(benzo[*d*]thiazol-2-yl)-2-phenylethyl)carbamate (entry 13, Table 4.1.4)



Yield: 328 mg (69%); white solid; R_f = 0.40 (EtOAc:Hexane, 2.5:7.5); mp: 141-142 °C; $[\alpha]_D^{25}$ = + 6.4 ($CHCl_3$, c = 0.50); ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.00 (d, *J* = 6.0 Hz, 1H), 7.80 (d, *J* = 12.0 Hz, 1H), 7.74 (m, 2H), 7.55-7.45 (m, 3H), 7.36 (d, *J* = 6 Hz, 3H), 7.25-7.20 (m, 6H), 7.13 (d, *J* = 6.0 Hz, 1H), 5.76 (br, NH), 5.45 (d, *J* = 6.0 Hz, 1H), 4.39 (d, *J* = 12.0 Hz, 2H), 4.16 (t, *J* = 6.0 Hz, 1H), 3.42 (d, *J* = 6.0 Hz, 1H), 3.33 ppm (d, *J* = 6.0 Hz, 1H);

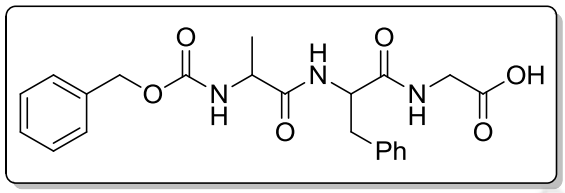
^{13}C NMR (150 MHz, $CDCl_3$): δ 172.4, 155.8, 153.2, 143.9, 141.4, 136.2, 135.0, 129.6, 128.8, 127.8, 127.2, 126.3, 125.3, 125.2, 123.1, 121.9, 120.1, 67.1, 54.9, 47.3, 41.2 ppm; IR (KBr): 3326, 3063, 2958, 1692, 1528, 1449, 1249, 1034, 758, 704 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{30}H_{25}N_2O_2S$ 477.1632, found 477.1632; Anal. Calcd for $C_{30}H_{24}N_2O_2S$: C, 75.60; H, 5.08; N, 5.88; S, 6.73; found: C, 75.68; H, 5.02; N, 5.90; S, 6.72.

(9*H*-Fluoren-9-yl)methyl (1-(benzo[*d*]thiazol-2-yl)-2-methylpropyl) carbamate (entry 14, Table 4.1.4)



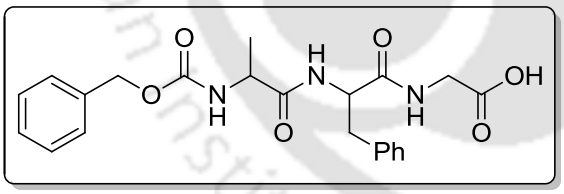
Yield: 265 mg (62%); white solid; R_f = 0.50 (EtOAc:Hexane, 3.0:7.0); ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.00 (d, *J* = 6.0 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.76 (d, *J* = 8.2 Hz, 2H), 7.64-7.61 (m, 2H), 7.48 (t, *J* = 6.0 Hz, 1H), 7.42-7.38 (m, 3H), 7.30 (d, *J* = 6.0 Hz, 2H), 5.68 (br, NH), 5.04 (t, *J* = 6.0 Hz, 1H), 4.46 (d, *J* = 6.0 Hz, 2H), 4.25 (t, *J* = 6.0 Hz, 1H), 2.46-2.43 (m, 1H), 1.03 (d, *J* = 6.0 Hz, 3H), 0.97 ppm (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 172.3, 156.4, 153.3, 143.9, 141.5, 134.9, 127.9, 127.3, 126.3, 125.3, 125.2, 123.2, 121.9, 120.2, 67.1, 59.2, 47.5, 29.9, 19.7, 17.7 ppm; IR (KBr): 3330, 3068, 2961, 1698, 1521, 1451, 1241, 1036, 751, 714 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{26}H_{25}N_2O_2S$ 429.1632, found 429.1637; Anal. Calcd for $C_{30}H_{24}N_2O_2S$: C, 72.87; H, 5.64; N, 6.54; S, 7.48; found: C, 72.90; H, 5.68; N, 6.58; S, 7.51.

Cbz-(L)Ala-(DL)Phe-Gly-OH



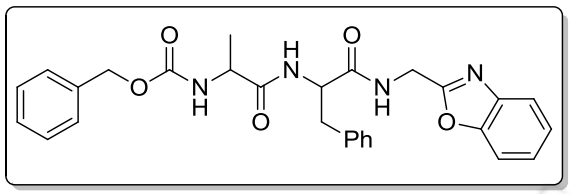
Yield: 256 mg (60%); white powder; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.27-7.22 (m, 5H), 7.20-7.14 (m, 2H), 7.10-7.08 (m, 3H), 5.64 (br, NH), 5.05 (s, 2H), 4.64 (q, *J* = 6.0 Hz, 1H), 3.91 (d, *J* = 6.0 Hz, 2H), 3.70 (t, *J* = 6.0 Hz, 1H), 3.20 (dd, *J* = 6.0, 6.0 Hz, 2H), 1.12 ppm (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 173.5, 173.3, 171.8, 171.7, 156.5, 136.6, 136.1, 129.2, 128.5, 128.4, 128.2, 127.9, 126.9, 67.7, 54.0, 50.8, 41.0, 37.6, 18.0 ppm; IR (KBr): 3340, 3031, 2971, 1690, 1600, 1535, 1457, 1255, 1081, 698 cm^{-1}; HLMS (ESI): m/z $[M+H]^+$ calcd for $C_{22}H_{26}N_3O_6$ 428.1816, found 428.1930; Anal. Calcd for $C_{23}H_{20}N_2O_3$: C, 61.82; H, 5.90; N, 9.83; found: C, 61.88; H, 5.91; N, 9.77.

Cbz-(L)Ala-(L)Phe-Gly-OH



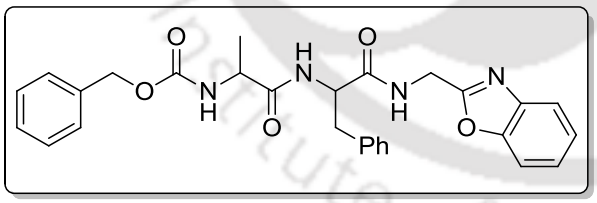
Yield: 235 mg (55%); white powder; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.31-7.27 (m, 5H), 7.20-7.18 (m, 2H), 7.16-7.10 (m, 3H), , 5.84 (br, NH), 5.01 (s, 2H), 4.84 (q, *J* = 6.0 Hz, 1H), 4.24 (t, *J* = 6.0 Hz, 1H), 3.95 (d, *J* = 8.0 Hz, 2 H), 3.14 ppm (dd, *J* = 6.0, 6.0 Hz, 2H), 1.20 (d *J* = 6.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 173.5, 172.4, 170.5, 156.4, 136.5, 136.1, 129.5, 128.8, 128.7, 128.6, 128.4, 127.0, 126.9, 67.8, 54.2, 50.8, 41.4, 38.1, 18.5 ppm; IR (KBr): 3338, 3032, 2970, 1690, 1602, 1532, 1457, 1264, 1080, 970 cm^{-1}; HLMS (ESI): m/z $[M+H]^+$ calcd for $C_{22}H_{26}N_3O_6$ 428.1816, found 428.1848; Anal. Calcd for $C_{23}H_{20}N_2O_3$: C, 61.82; H, 5.90; N, 9.83; found: C, 61.87; H, 5.94; N, 9.76.

Benzoxazole of Cbz-(L)Ala-(DL)Phe-Gly-OH



Yield: 207 mg (70%); white solid; R_f = 0.40 (EtOAc:Hexane, 3.0:7.0); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, *J* = 8.0 Hz, 1H), 7.61 (d, *J* = 4.0 Hz, 1H), 7.36-7.34 (m, 4H), 7.31-7.30 (m, 5H), 7.10-7.08 (m, 3H), 6.65 (br, NH), 5.11 (s, 2H), 4.51 (q, *J* = 6.0 Hz, 1H), 4.42 (d, *J* = 6 Hz, 1H), 4.31 (d, *J* = 4.0 Hz, 2H), 3.16 (dd, *J* = 4.0, 4.0 Hz, 2H), 1.24 ppm (d, *J* = 4.0 Hz, 3H);^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 171.4, 156.1, 151.1, 144.0, 135.8, 132.4, 129.5, 128.8, 128.7, 128.2, 127.3, 125.1, 124.7, 123.6, 120.1, 118.6, 109.8, 67.3, 53.4, 50.5, 37.9, 29.9, 14.2 ppm; IR (KBr): 3336, 3032, 2924, 1690, 1602, 1531, 1457, 1265, 1080, 750, 690 cm^{-1}; LRMS (ESI): m/z $[M+H]^+$ calcd for $C_{28}H_{29}N_4O_5$ 501.2132, found 501.2052; Anal. Calcd for $C_{28}H_{28}N_4O_5$: C, 67.05; H, 5.83; N, 11.17; found: C, 67.10; H, 5.87; N, 11.10.

Benzoxazole of Cbz-(L)Ala-(L)Phe-Gly-OH



Yield: 207 mg (70%); white solid; R_f = 0.40 (EtOAc:Hexane, 3.0:7.0); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.82 (d, *J* = 12.0 Hz, 1H), 7.65 (d, *J* = 6.0 Hz, 1H), 7.37-7.32 (m, 5H), 7.31-7.29 (m, 4H), 7.11-7.07 (m, 3H), 5.10 (s, 2H), 4.50 (q, *J* = 6.0 Hz, 1H), 4.44 (d, *J* = 6.0 Hz, 1H), 4.32 (d, *J* = 6.0 Hz, 2H), 3.11 (dd, *J* = 6.0, 6.0 Hz, 2H), 1.22 ppm (d, *J* = 4.0 Hz, 3H);^{13}C NMR (150 MHz, $CDCl_3$): δ 171.9, 171.4, 156.2, 151.1, 144.1, 142.1, 139.4, 135.6, 132.2, 130.1, 128.7, 128.4, 128.2, 127.3, 125.0, 124.6, 123.6, 120.1, 118.7, 109.9, 67.2, 53.4, 50.6, 38.0, 29.0, 14.3 ppm; IR (KBr): 3338, 3028, 2922, 1690, 1612, 1530, 1461, 1267, 1081, 752, 692

cm^{-1}; LRMS (ESI): m/z $[M+H]^+$ calcd for $C_{28}H_{29}N_4O_5$ 501.2132, found 501.2161; Anal. Calcd for $C_{28}H_{28}N_4O_5$: C, 67.05; H, 5.83; N, 11.17; found: C, 67.11; H, 5.88; N, 11.09.

4.7. Selected spectra

4.7.1. ^{1}H-NMR and ^{13}C-NMR spectra of compounds

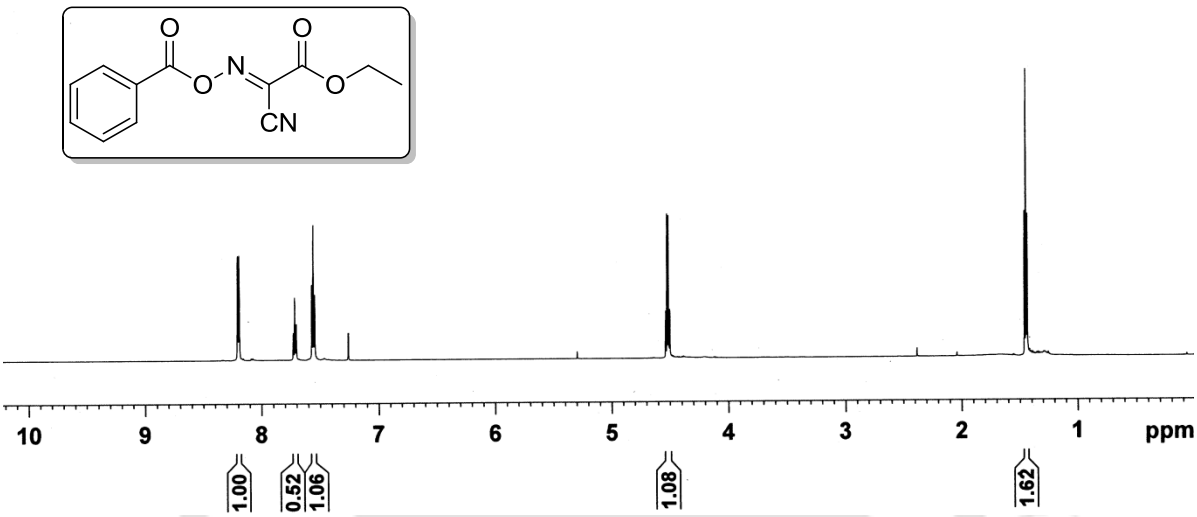


Figure S1: ^{1}H-NMR spectrum of the intermediate III

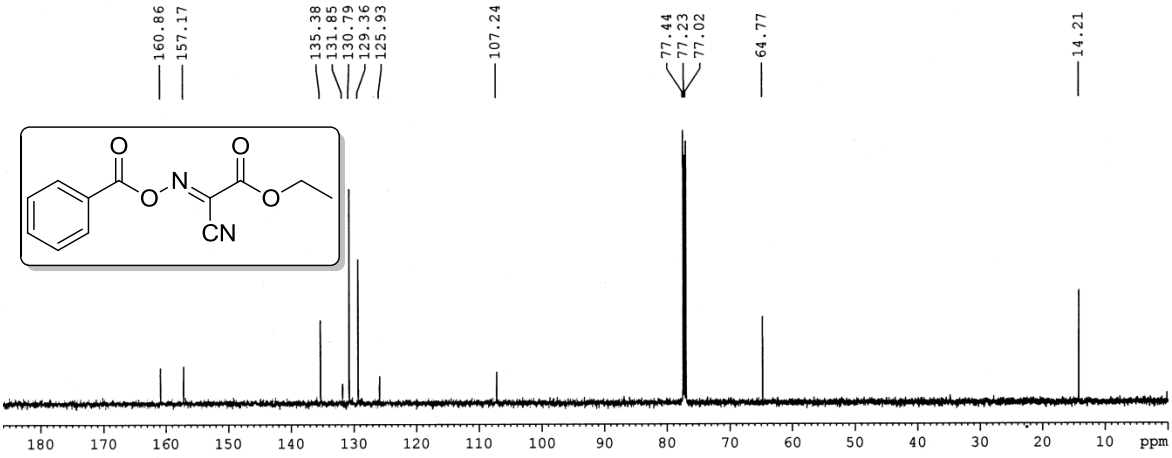


Figure S2: ^{13}C-NMR spectrum of the intermediate III

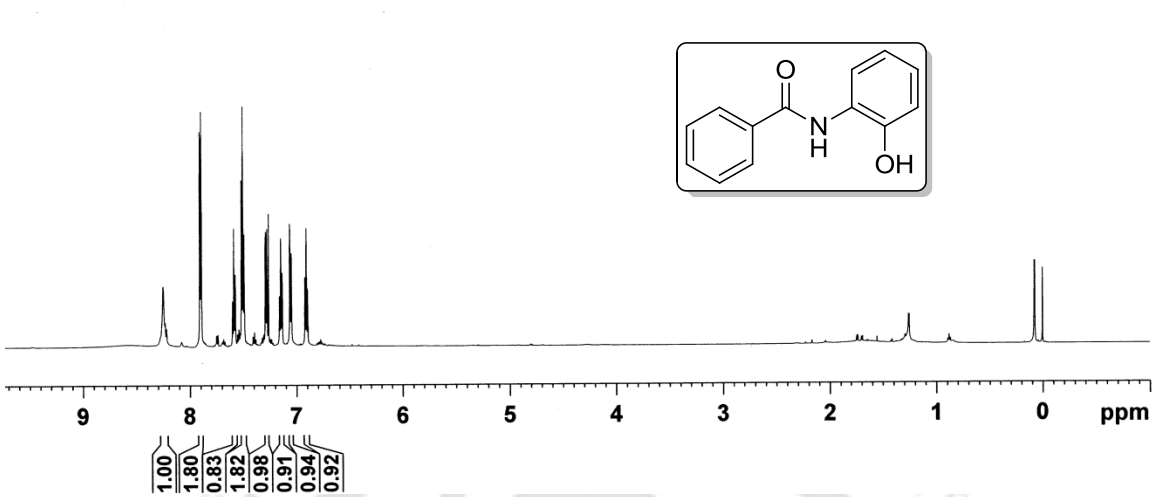


Figure S3: ^{1}H-NMR spectrum of the intermediate IV

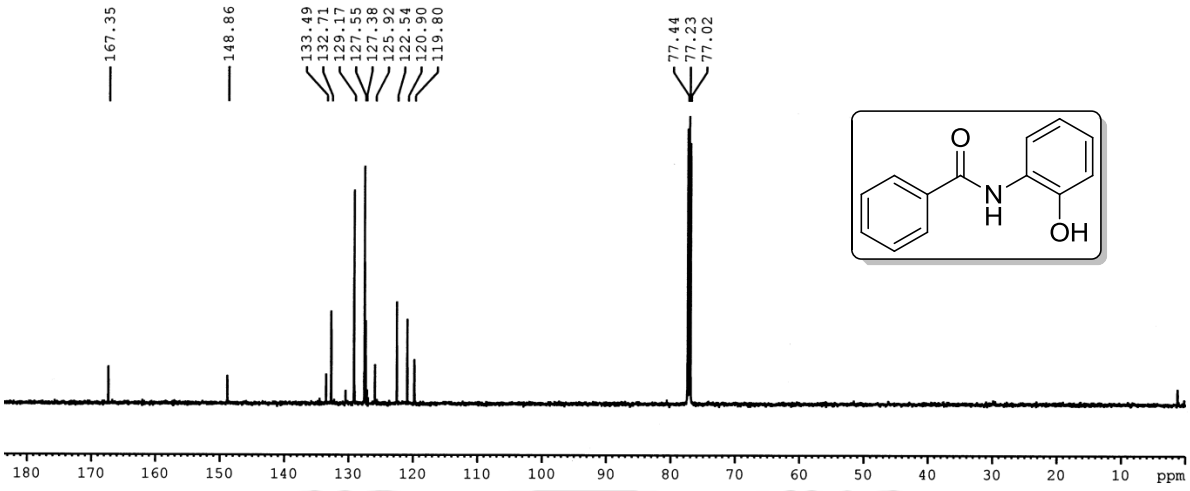


Figure S4: ^{13}C-NMR spectrum of the intermediate IV

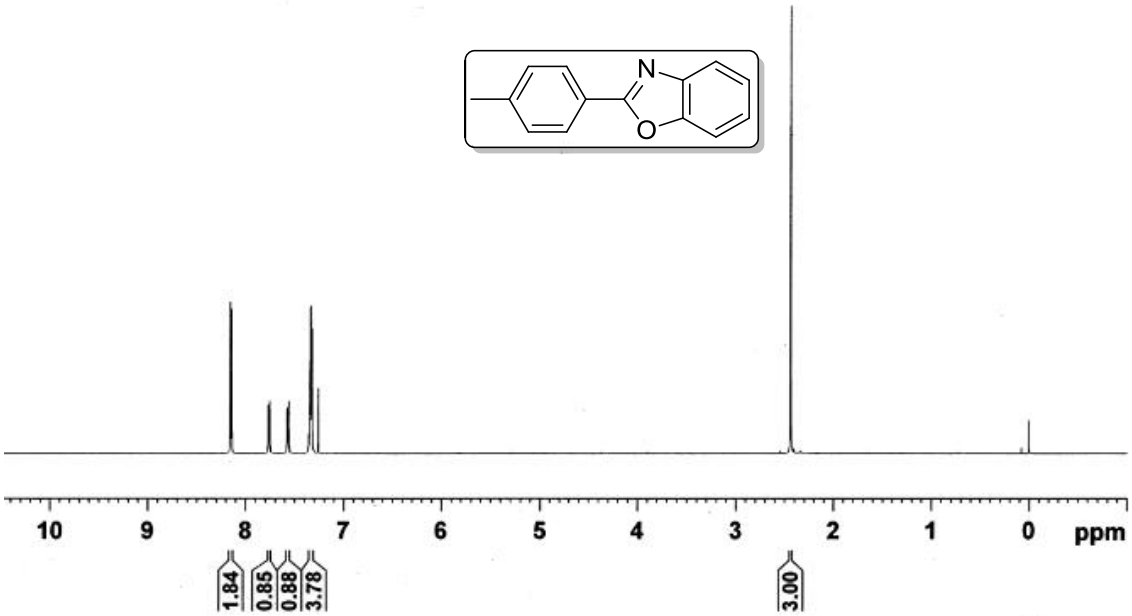


Figure S5: [1]H-NMR spectrum of. 2-(*p*-tolyl)benzo[d]oxazole (entry 3, Table 4.1.2)

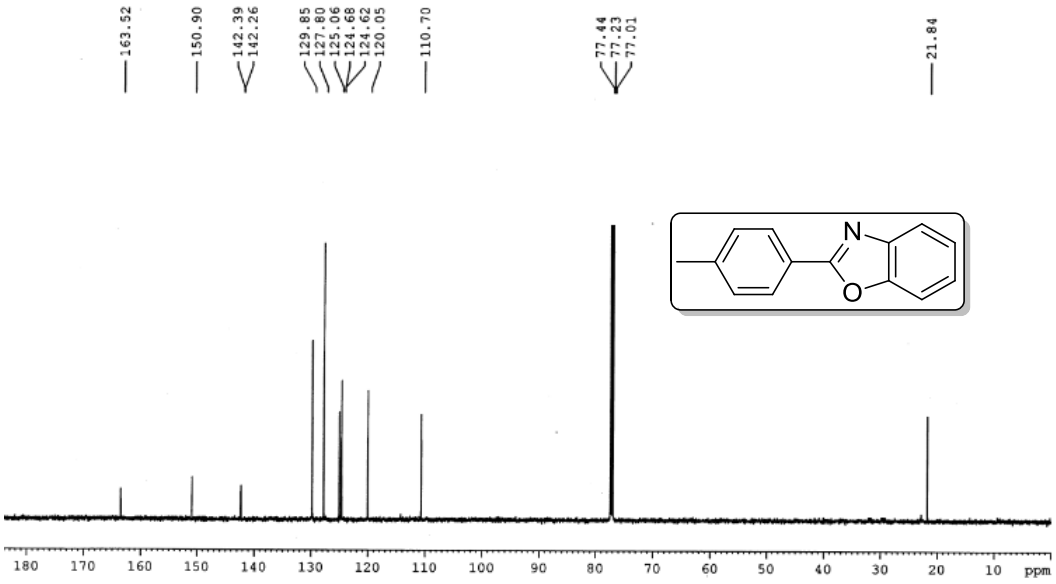


Figure S6: [13]C-NMR spectrum of 2-(*p*-tolyl)benzo[d]oxazole (entry 3, Table 4.1.2).

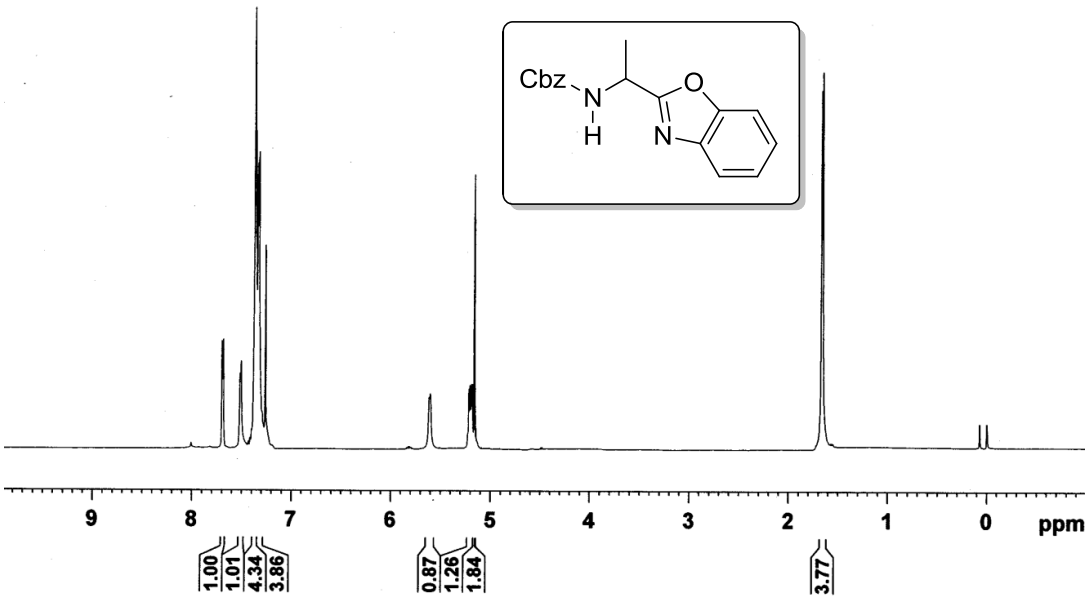


Figure S7: ^{1}H-NMR spectrum of benzyl (1-(benzo[d]oxazol-2-yl)ethyl)carbamate (entry 1, Table 4.1.4).

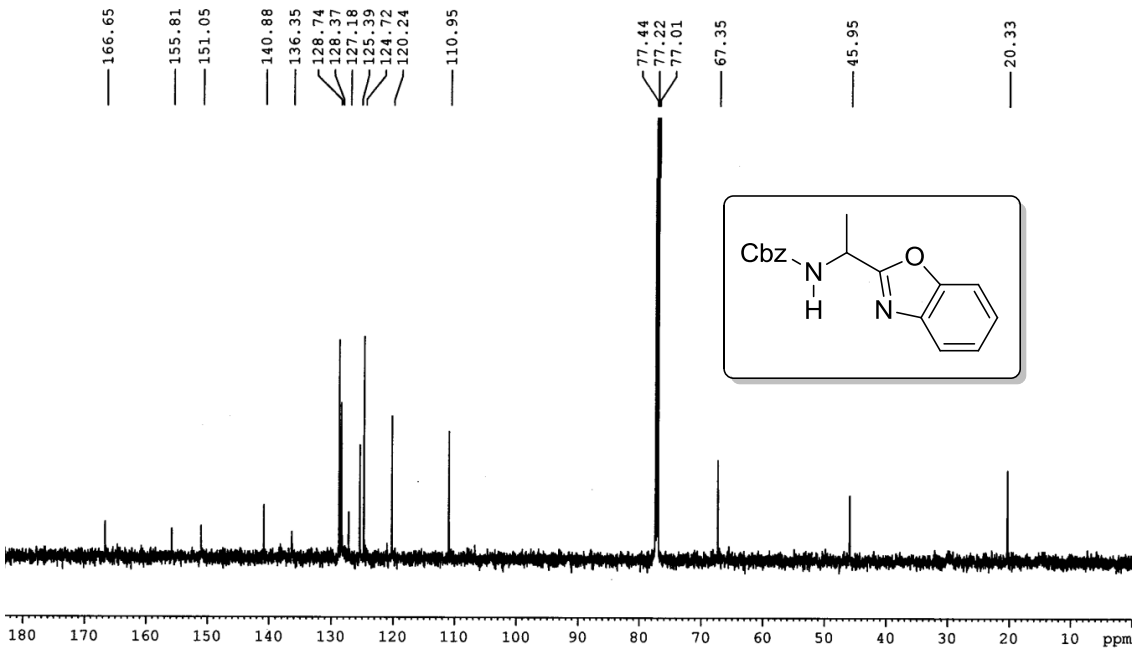


Figure S8: ^{13}C-NMR spectrum of benzyl (1-(benzo[d]oxazol-2-yl)ethyl)carbamate (entry 1, Table 4.1.4).

4.7.2. HPLC chromatograms and mass spectra of SPPS product

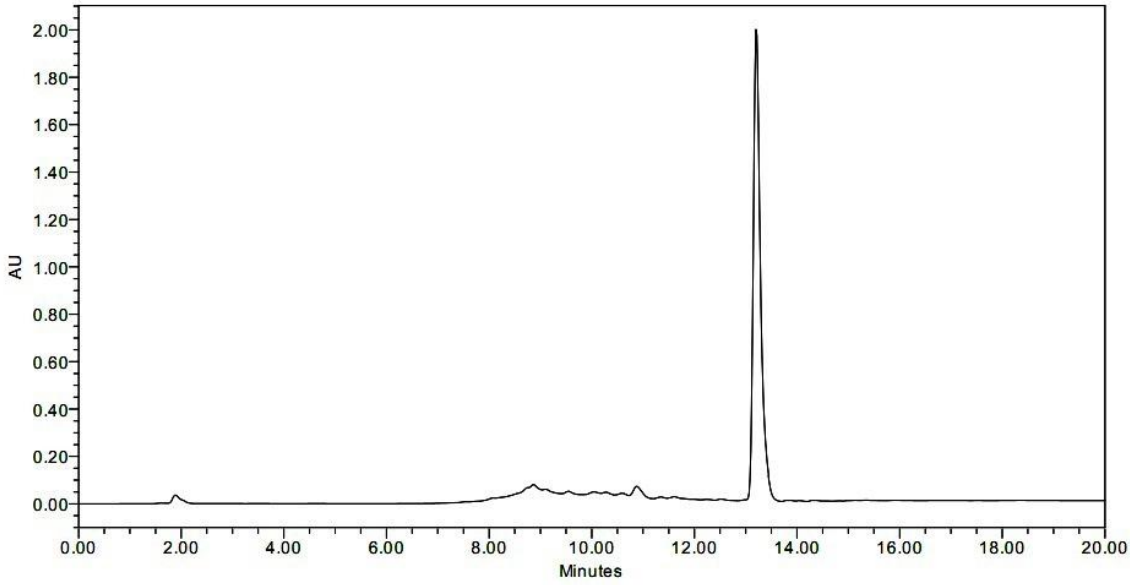


Figure S9: HPLC chromatogram of free carboxylic acid of adipic acid of NFGAILG-NH_2, analyzed by reverse phase HPLC, symmetry C18 analytical column, with linear gradient of 20 min (5 to 100 % acetonitrile in water with 0.09 % TFA).

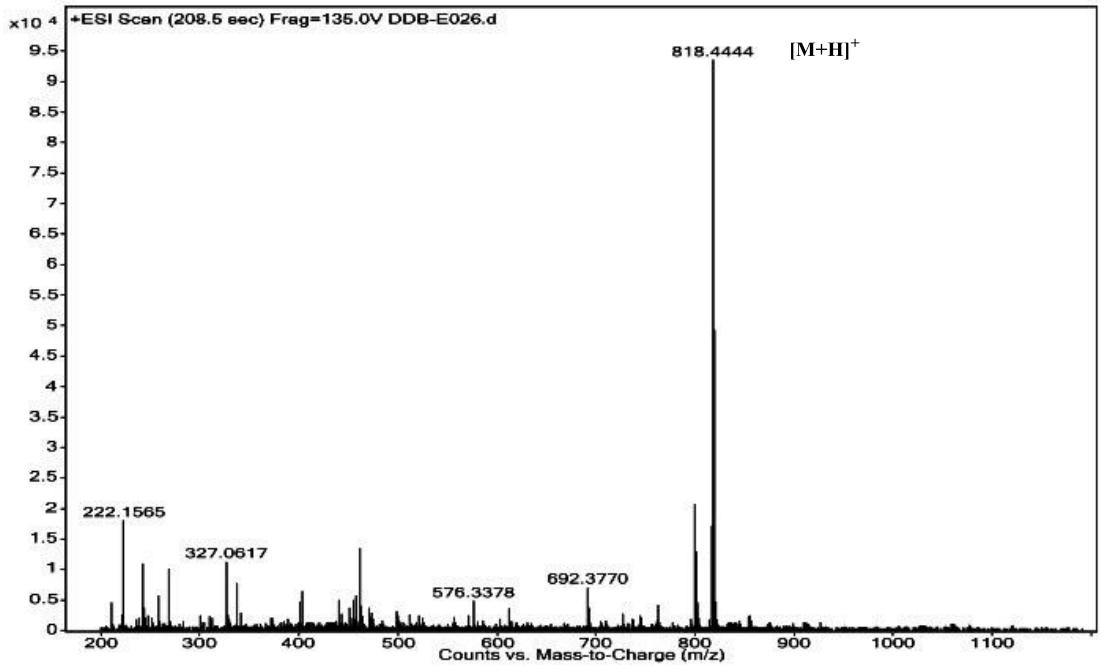


Figure S10: ESI-MS spectrum of the free carboxylic acid of adipic acid of NFGAILG-NH_2.

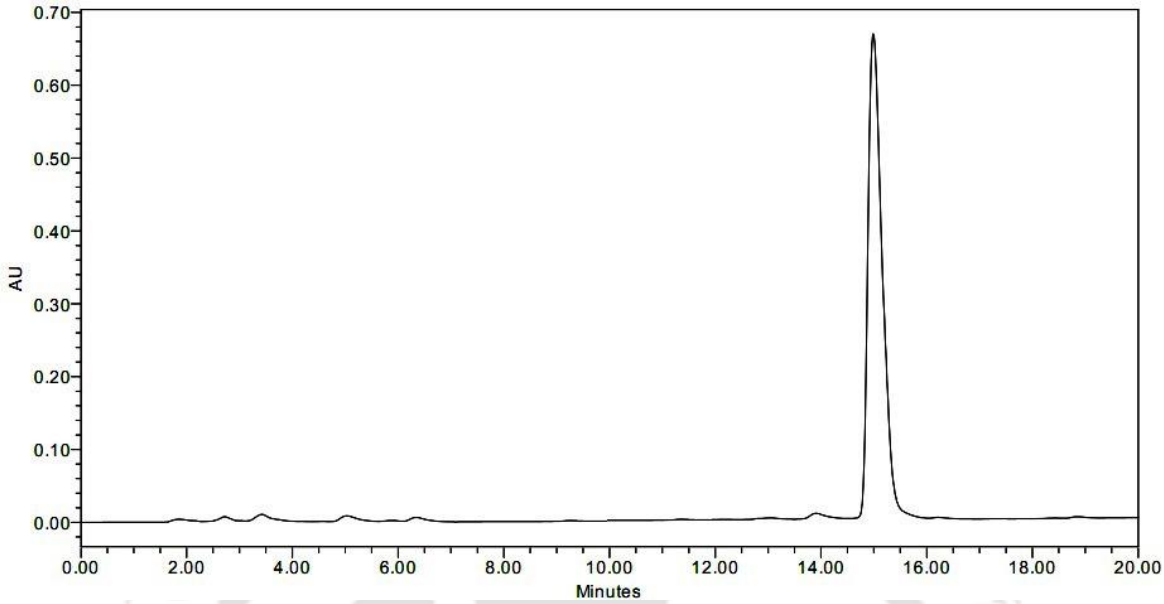


Figure S11: HPLC chromatogram of Benzoxazole of Adioyl NFGAILG-NH_2, analyzed by reverse phase HPLC, symmetry C18 analytical column, with linear gradient of 20 min (5 to 100 % acetonitrile in water with 0.09 % TFA).

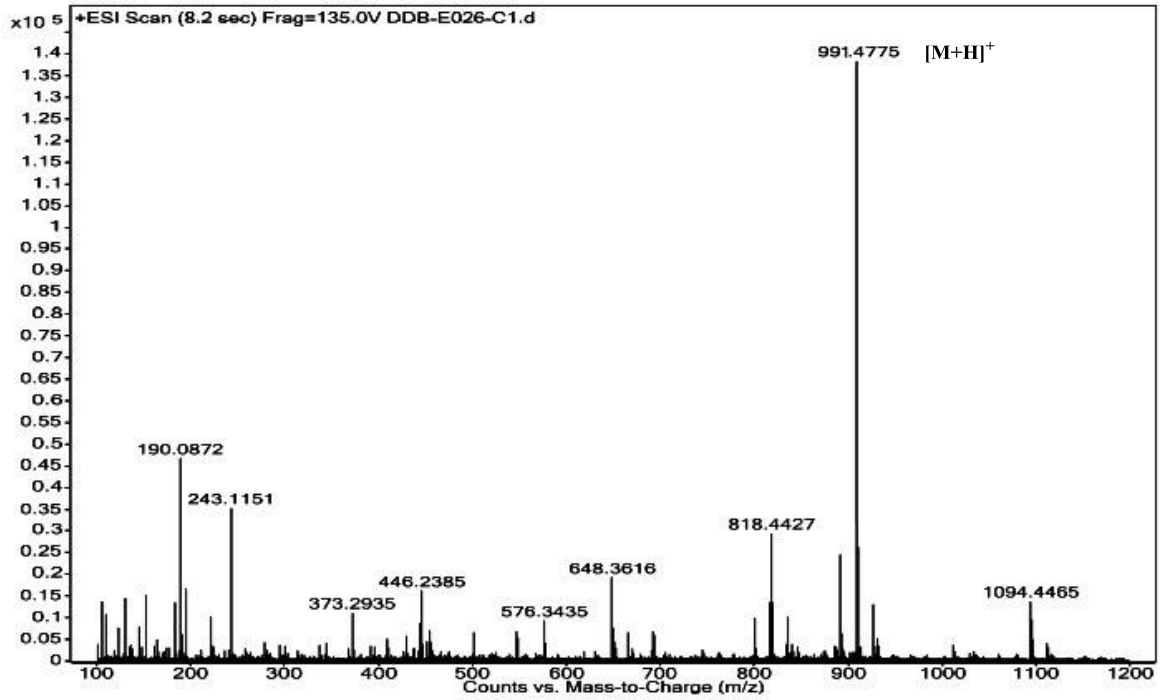


Figure S12: ESI-MS spectrum of the Benzoxazole of Adioyl NFGAILG-NH_2.

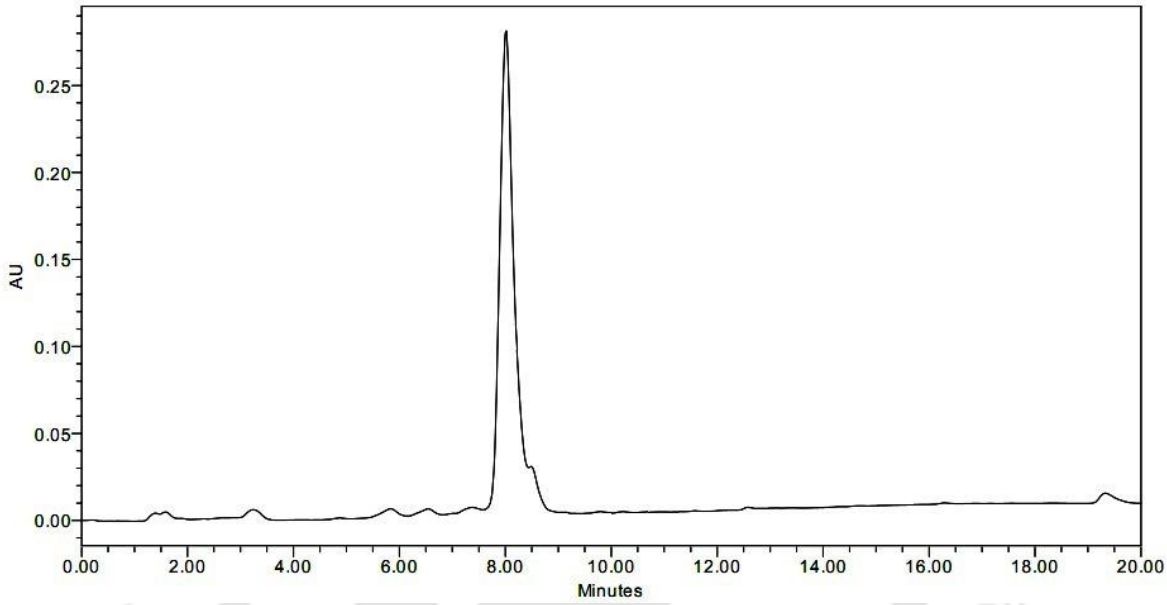


Figure S13: HPLC chromatogram of free side chain of Aspartic acid of Fmoc-DVFFAG-NH_2, analyzed by reverse phase HPLC, symmetry C18 analytical column, with linear gradient of 20 min (40 to 100 % for 0 to 10 min, then 100% upto 20 min, acetonitrile in water with 0.09 % TFA)

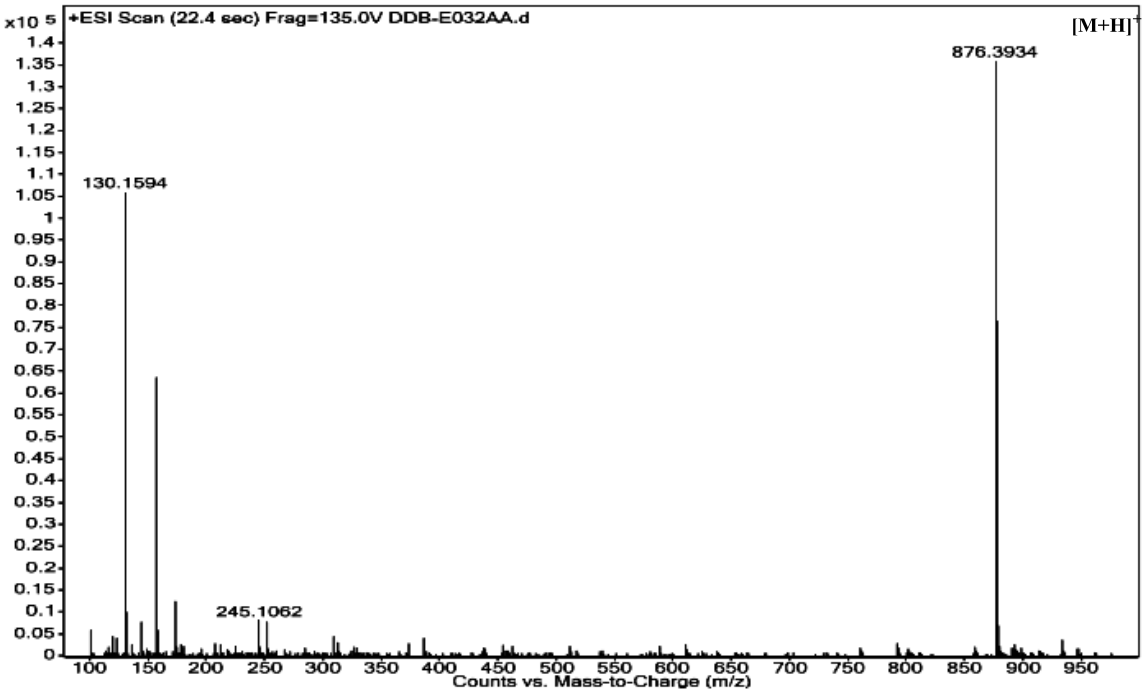


Figure S14: ESI-MS spectrum of the free side chain of Aspartic acid of Fmoc-DVFFAG-NH_2.

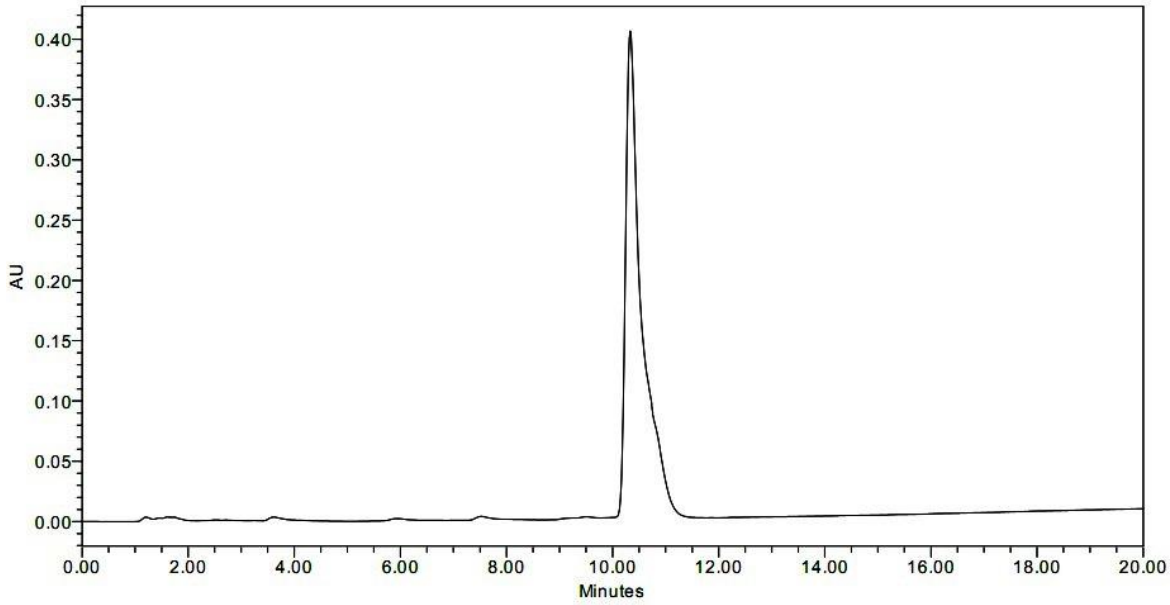


Figure S15: HPLC chromatogram of Benzoxazole of side chain of Aspartic acid of Fmoc-DVFFAG-NH_2, analyzed by reverse phase HPLC, symmetry C18 analytical column, with linear gradient of 20 min (40 to 100 % for 0 to 10 min, then 100% upto 20 min, acetonitrile in water with 0.09 % TFA).

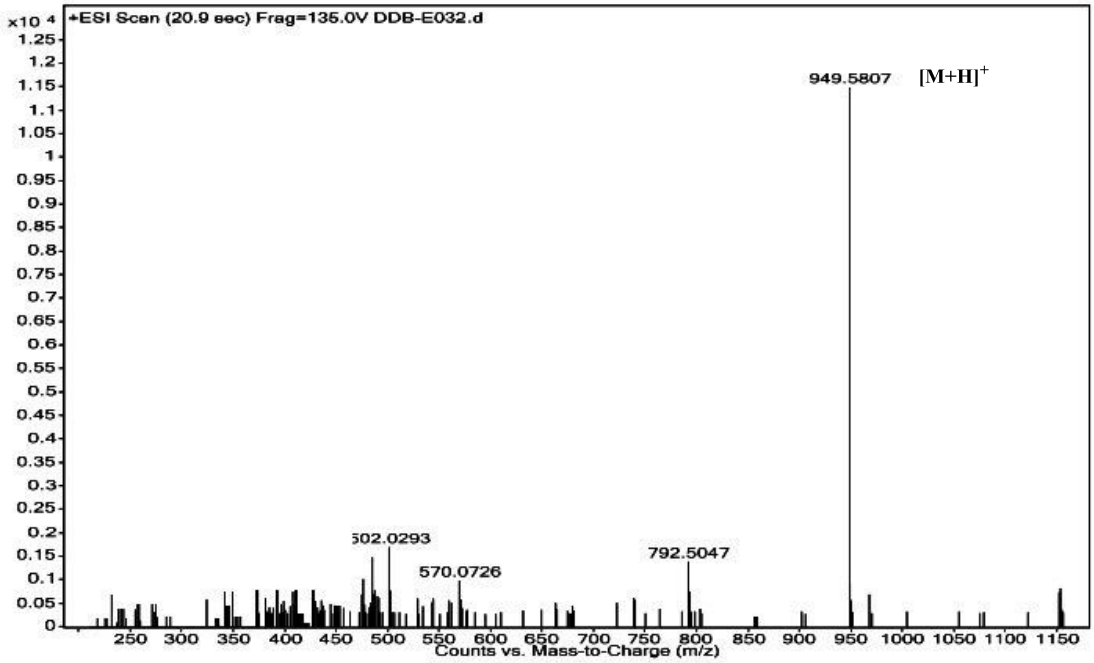
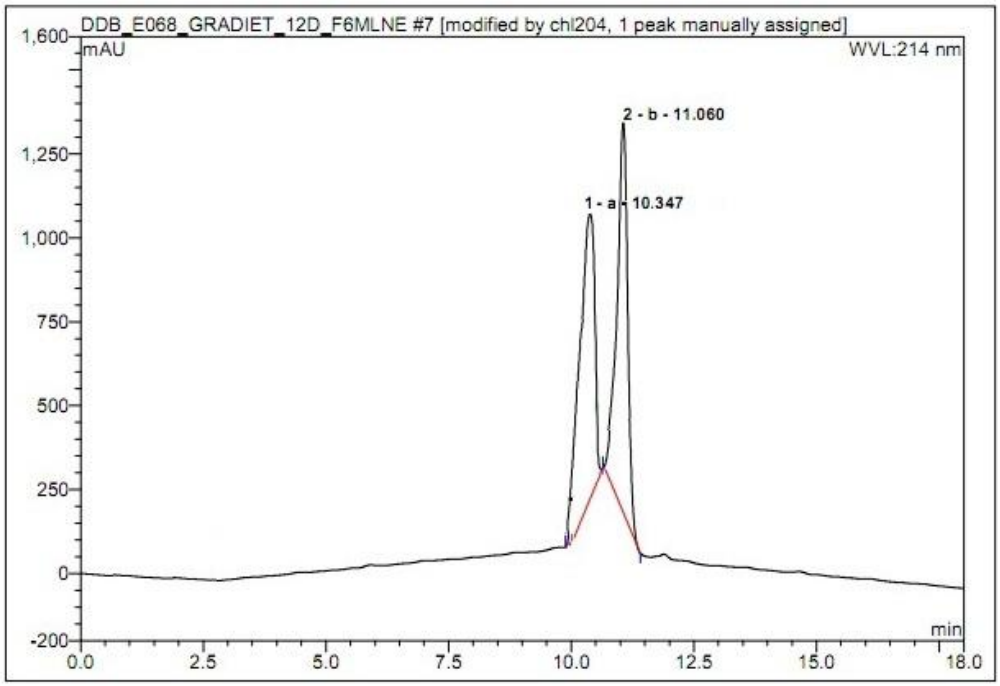


Figure S16: ESI-MS spectrum of the Benzoxazole of side chain of Aspartic acid of Fmoc-DVFFAG-NH_2.



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	10.34	a	1003.756	259.124	48.83	n.a.	BMB*^
2	11.06	b	1161.865	300.666	51.17	n.a.	BMB*
Total:			2165.621	559.790	100.00	0.000	

Figure S17: HPLC chromatogram of Cbz-(L)Ala-(DL)Phe-Gly-OH, analyzed by reverse phase HPLC, symmetry C18 analytical column, with linear gradient of 20 min (5 to 60 % for 0 to 8 min, then 60 to 100% upto 18 min, acetonitrile in water with 0.09 % TFA)

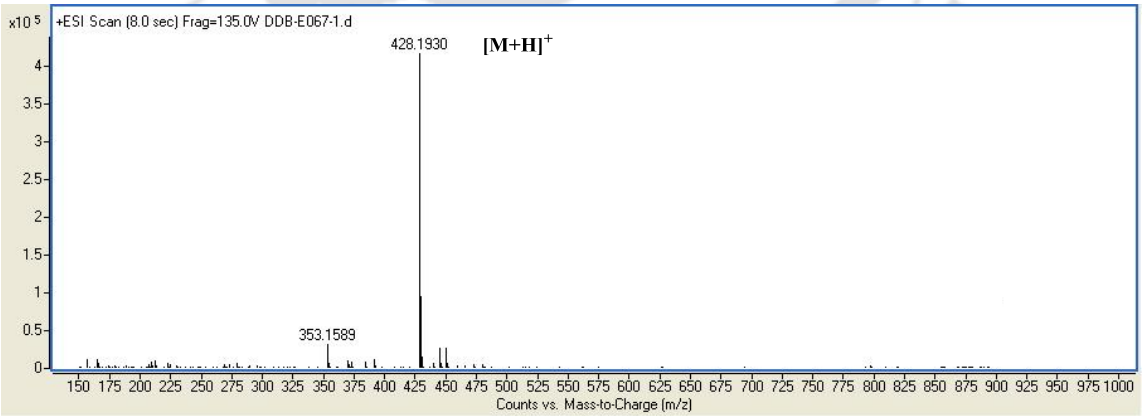


Figure S18: ESI-MS spectrum of Cbz-(L)Ala-(DL)Phe-Gly-OH, peak retention time 10.35 min of above chromatogram.

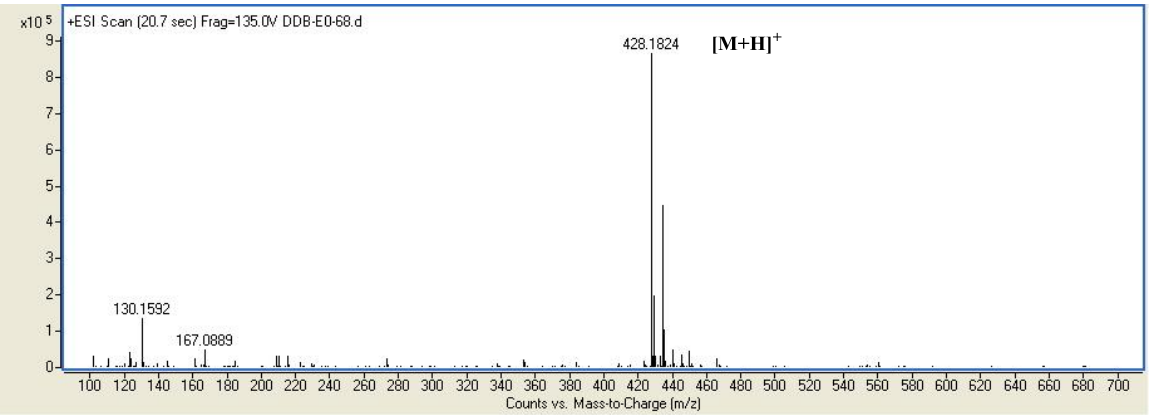
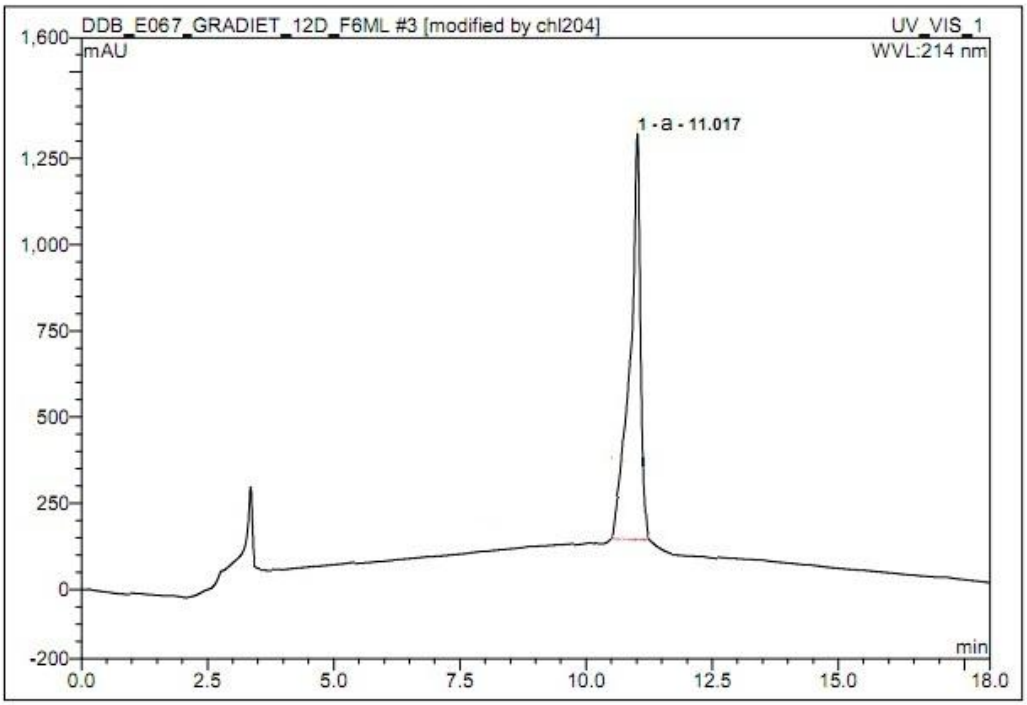


Figure S19: ESI-MS spectrum of Cbz-(L)Ala-(DL)Phe-Gly-OH, peak retention time 11.06 min of above chromatogram.



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	11.02	a	1186.810	240.012	100.00	n.a.	BMb*
Total:			1186.810	240.012	100.00	0.000	

Figure S20: HPLC chromatogram of Cbz-(L)Ala-(L)Phe-Gly-OH, analyzed by reverse phase HPLC, symmetry C18 analytical column, with linear gradient of 20 min (5 to 60 % for 0 to 8 min, then 60 to100% upto 18 min, acetonitrile in water with 0.09 % TFA)

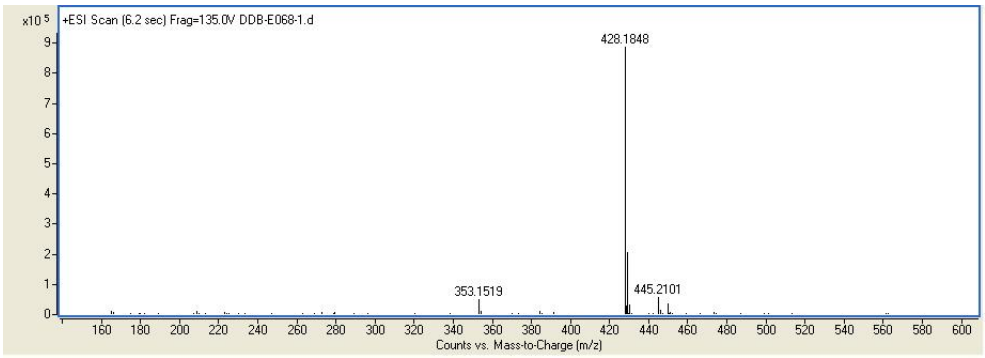
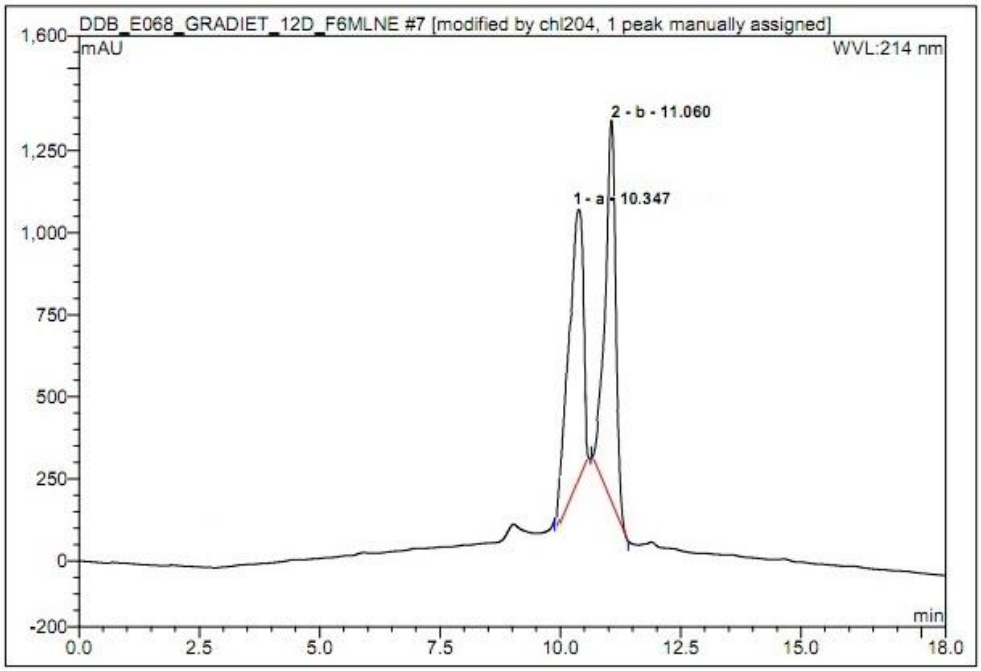


Figure S21: ESI-MS spectrum of Cbz-(L)Ala-(L)Phe-Gly-OH, peak retention time 11.01 min of above chromatogram.



No.	Ret.Time min		Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	10.34	a		1003.756	259.124	48.83	n.a.	BMB*^
2	11.06	b		1161.865	300.666	51.17	n.a.	BMB*
Total:				2165.621	559.790	100.00	0.000	

Figure S22: HPLC chromatogram of benzoxazole of Cbz-(L)Ala-(DL)Phe-Gly-OH, analyzed by reverse phase HPLC, symmetry C18 analytical column, with linear gradient of 20 min (5 to 60 % for 0 to 8 min, then 60 to100% upto 18 min, acetonitrile in water with 0.09 % TFA)

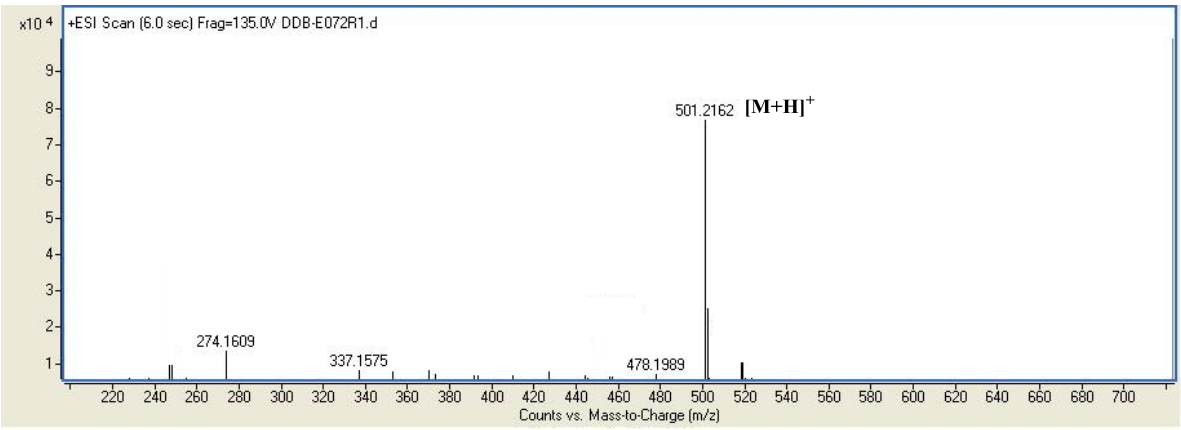


Figure S23: ESI-MS spectrum of benzoxazole of Cbz-(L)Ala-(DL)Phe-Gly-OH, peak retention time 11.49 min of above chromatogram.

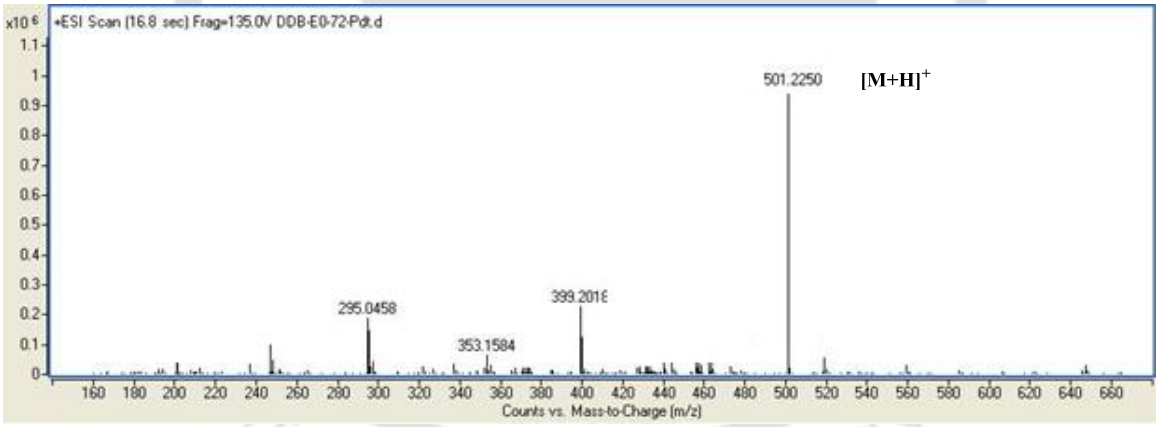
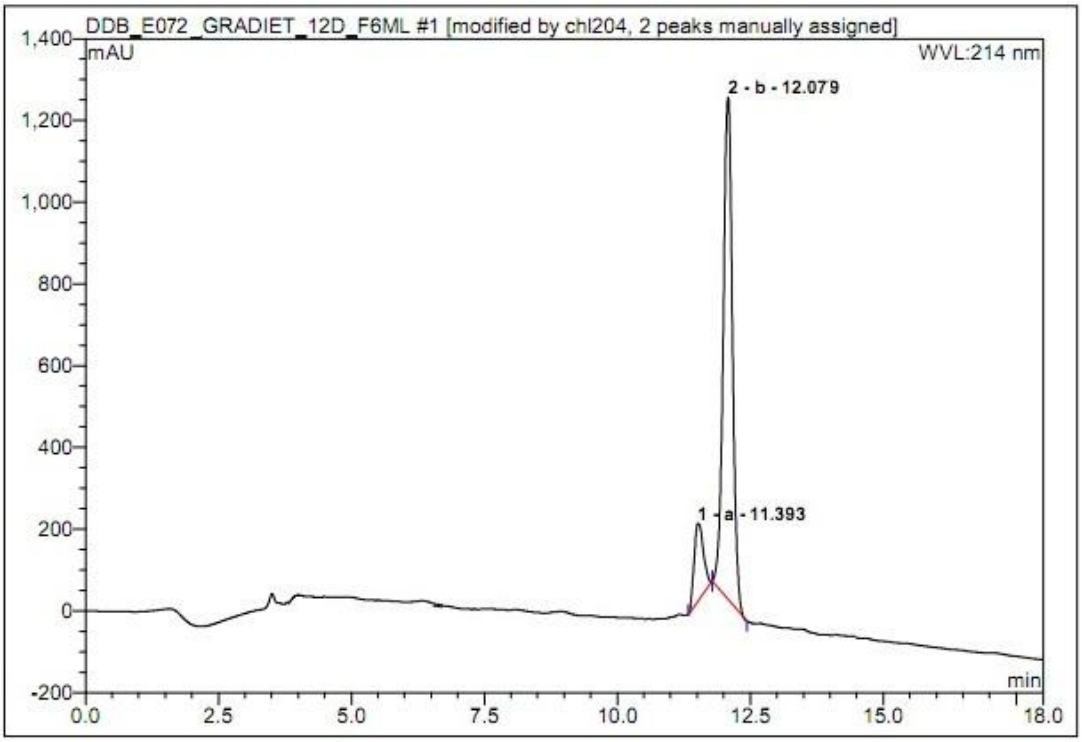


Figure S24: ESI-MS spectrum of benzoxazole of Cbz-(L)Ala-(DL)Phe-Gly-OH, peak retention time 12.07 min of above chromatogram.



No.	Ret.Time min		Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	11.39	a		76.549	15.343	05.39	n.a.	BMb*^
2	12.08	b		1342.156	269.261	94.61	n.a.	bMB*^
Total:				1418.705	284.604	100.00	0.000	

Figure S25: HPLC chromatogram of benzoxazole of Cbz-(L)Ala-(L)Phe-Gly-OH, analyzed by reverse phase HPLC, symmetry C18 analytical column, with linear gradient of 20 min (5 to 60 % for 0 to 8 min, then 60 to100% upto 18 min, acetonitrile in water with 0.09 % TFA)

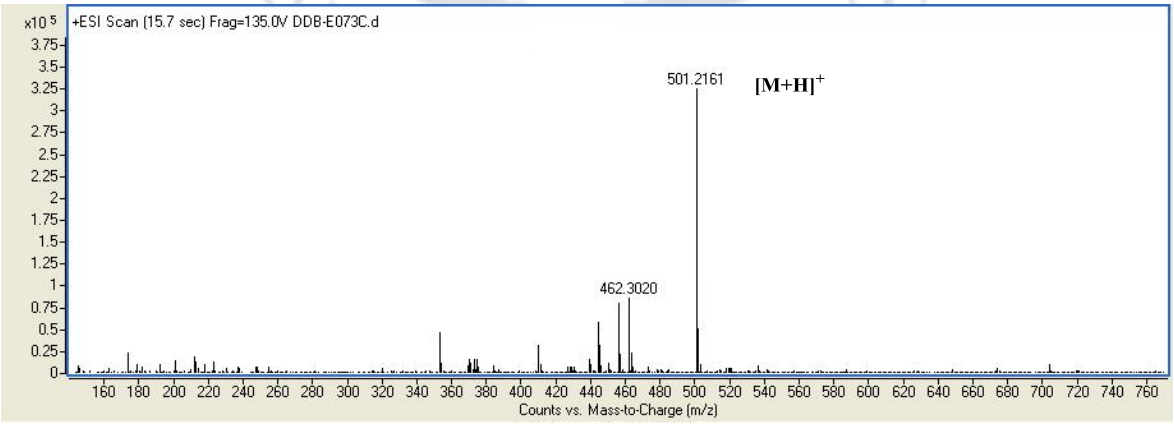


Figure S26: ESI-MS spectrum of benzoxazole of Cbz-(L)Ala-(L)Phe-Gly-OH, peak retention time 11.39 min of above chromatogram.

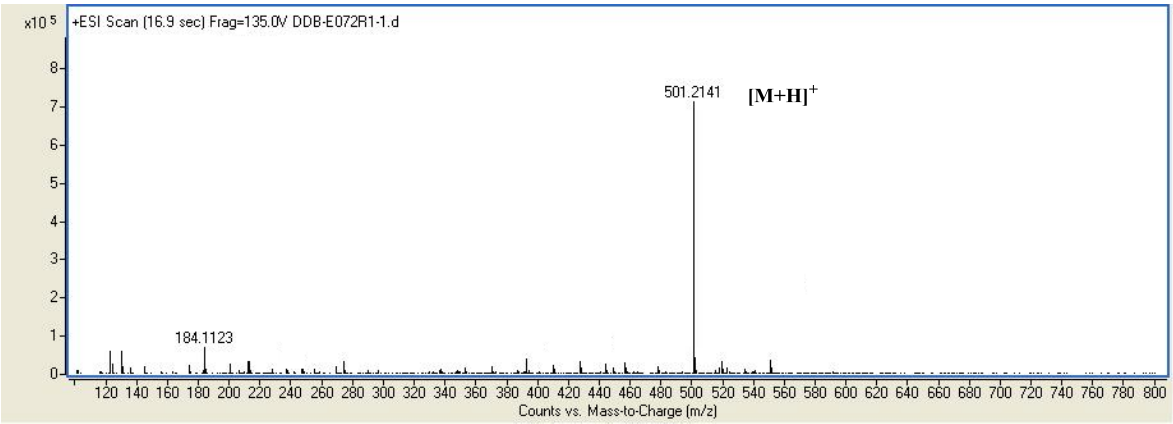
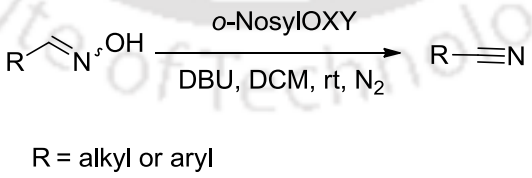


Figure S27: ESI-MS spectrum of benzoxazole of Cbz-(L)Ala-(L)Phe-Gly-OH, peak retention time 12.07 min of above chromatogram.

Chapter 5: Synthesis of Nitrile from Aldoxime in Presence of Ethyl 2-cyano-2-(2-nitrobenzene sulfonyloxyimino)acetate (*o*-NosylOXY)

In this chapter, we demonstrated the application of the reagent (*o*-NosylOXY) for the synthesis nitrile from aldoxime. Nitriles are important synthons in organic syntheses as they are involved in many functional group transformations and medicinally active molecules (Chapter 1, section 1.3.4). There are several methods reported for the synthesis of nitrile (Chapter 1, section 1.7). Most of those reported methods have some drawbacks, including high temperature, longer reaction time and use of metal catalyst. Herein, we have developed a new method of nitrile synthesis from aldoxime using *o*-NosylOXY at room temperature (*Scheme 5.1*). A mechanistic investigation was also performed.



Scheme 5.1. Synthesis of nitrile using *o*-NosylOXY

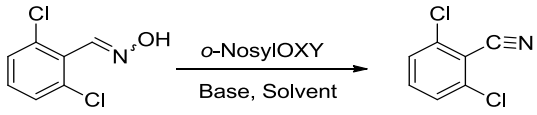
5.1. Optimization and substrates scope for the synthesis of nitrile

For model reaction, we took 2, 6-dichlorobenzaldoxime (1 equiv), and *o*-NosylOXY (1 equiv) in the presence of triethylamine (3 equiv) in dichloromethane. Interestingly, the reaction was completed within 1h, with isolated yield of 80%. Inspired by that result, we went on to standardize the reaction.

For optimization of base, we performed the same model reaction with different bases as shown in table 5.1.1 and observed that in presence of tertiary amine as base, the reaction went to completion smoothly and furnished the product in very good yield in all the cases except with 2,4,6-collidine and 2,3,5-collidine. We observed, in presence of DBU and DABCO the reaction was completed in lesser time (*entry 3 & 11, Table 5.1.1*). Therefore, we decided to proceed further with DBU. It was important to note that the formation of the product in the absence of any base was not observed.

Next, we investigated the stoichiometry of the base using different equivalents of DBU. We noted that 2.5 equiv was compulsory for completion of the reaction. The conversion was not completed with lesser amount of base and resulted in the desired product with reduced yield (*Table 5.1.1*). However, the unreacted starting material could be recovered. It was confirmed that the ratio of the base to the substrate should be 2.5:1 so that the reaction gets completed within 10 min. Various solvents were screened, such as hexane, ethyl acetate, acetone, dichloromethane and methanol (*entry 11-15, Table 5.1.1*). Experiments revealed that dichloromethane was the best solvent for that transformation. In methanol, there was a side product corresponding to the competitive reaction for the formation of the sulfonate ester of methanol.

Table 5.1.1. Optimization of reaction[a]

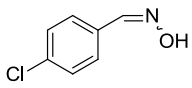
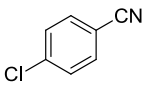
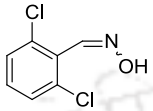
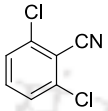
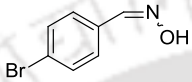
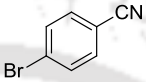
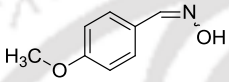
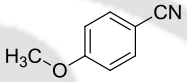
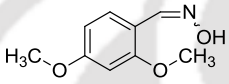
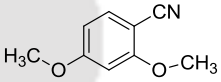
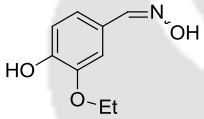
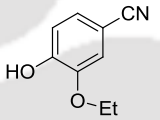
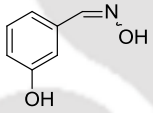
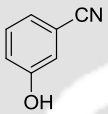
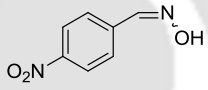
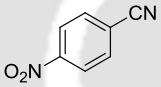
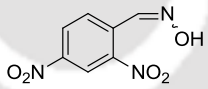
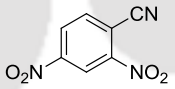
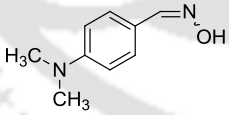
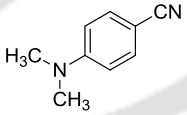
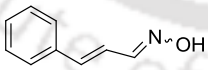
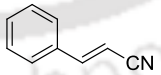
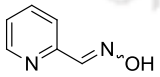
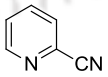
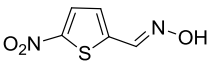
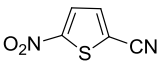
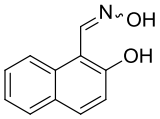
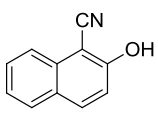


Entry	Base	Solvent	Equiv of base	Time	Yield (%)[b]
1	DIPEA	DCM	2.5	6 h	60
2	TEA	DCM	2.5	50 min	80
3	DABCO	DCM	2.5	10 min	70
4	2,4,6-collidine	DCM	2.5	5 h	30
5	2,3,5-collidine	DCM	2.5	5 h	25
6	DBU	DCM	0.0	5 h	NR [b]
7	DBU	DCM	0.5	5 h	15
8	DBU	DCM	1.0	5 h	40
9	DBU	DCM	1.5	5 h	59
10	DBU	DCM	2.0	2 h	81
11	DBU	DCM	2.5	10 min	94
12	DBU	Methanol	2.5	6 h	30
13	DBU	Acetone	2.5	2 h	60
14	DBU	EtOAc	2.5	5 h	20
15	DBU	Hexane	2.5	4 h	20

[a]*Performed with 2,6-dichlorobenzaldehyde oxime (1 equiv), o-NosylOXY (1.5 equiv), room temperature.* [b]*Yields refer to the isolated yield after column chromatography.*

The current methodology was applicable to wide range of substrates (*Table 5.1.2*) and tolerates with various functional groups, such as NO_2, MeO-, EtO- *etc*. Under optimized conditions, all the substrates went to completion within 10 min and obtained the product in very good yield. There was no influence of electron donating groups, *e.g.* MeO-, EtO-, *etc*. or electron withdrawing group, *e.g.* NO_2 on the yield and dynamics of the reaction.

Table 5.1.2. Synthesis of various nitriles[a]

Entry	Substrate	Product	Yield [b]
1			93
2			94
3			92
4			82
5			87
6			79
7			89
8			89
9			87
10			78
11			86
12			85
13			83
14			79

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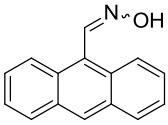
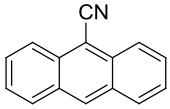
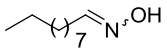
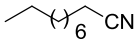
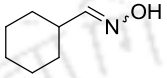
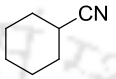
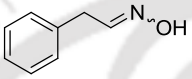
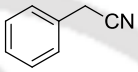
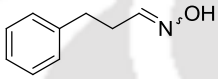
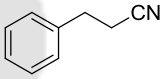
15			81
16			82
17			76
18			74
19			78

[a]*Performed with aldoxime (1 equiv), o-NosylOXY (1.5 equiv), and DBU (2.5 equiv) room temperature.* [b]*Yields refer to the isolated yield after column chromatography.*

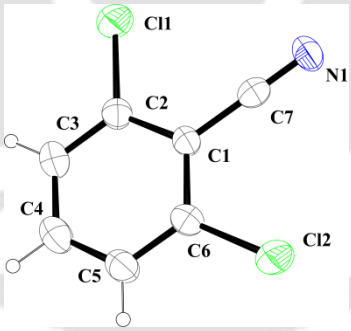


Figure 5.1.1. X-ray crystallographic structure of the product of entry 2 in table 5.1.2 (ORTEP diagram with ellipsoid of 50% probability, CCDC No. 905250)

The complicated substrates that include the conjugated aldoxime (*entry 11, 13 and 14, Table 5.1.2*) underwent the reaction to furnish the product with excellent yields. The important advantage of the protocol was that (*entry 11)* the stereochemistry was retained, *i.e.* ***E*** isomer of the aldehyde produced the ***E*** isomer of the corresponding nitrile unlike

the Wittig reaction which produces a mixture of ***E*** and ***Z*** isomers. The reaction worked well with aliphatic systems also (*entry 16-19, Table 5.1.2*).

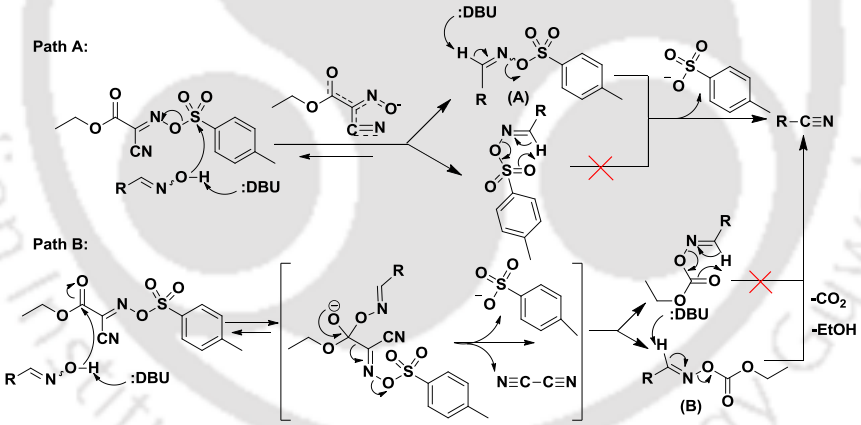
5.2. Mechanism study

To investigate the mechanism of the reaction (Scheme 5.2.1), we have taken 4-CH_3-C_6H_4-SO_3XY (**IIIa**) as reagent and TEA as base to slow down the reaction. Premature quenching (at 30 min) of the reaction, where *4*-chlorobenzaldoxime was used as substrate, resulted two products, which were finally characterized as the intermediates (E)-4-chlorobenzaldehyde-*O*-tosyloxime (**A**) and (E)-4-chlorobenzaldehyde-*O*-ethoxycarbonyl-oxime (**B**). Existence of these two intermediates in the reaction mixture indicated that the reaction might proceed following both of the probable mechanisms as depicted in scheme 5.2.1 as the path A and the path B.

In path A, the base deprotonates the aldoxime to generate a nucleophile which attacked the electrophilic center over sulphur of the reagent **IIIa** and forms sulfonate ester of aldoxime as intermediate **A**. Finally, second equiv of the base deprotonates the hydrogen on the ethylene carbon of the imine thereby expelled the 4-CH_3-C_6H_4-SO_2 group which was a good leaving group and resulted in the generation of the nitrile along with Oxyma (byproduct). We computed the charge distribution by Mulliken analysis for compound **IIIa** at B3LYP/6-31G (D, P) level of theory[136] and found that partial positive charge over the carbonyl carbon (0.59) of compound **IIIa** is much less than that over the sulphur center (1.29). Therefore, the path A was accepted as the favorable route of the reaction.

In path B, the base deprotonates the oxime proton in the aldoxime to generate a nucleophile, which attacked the electrophilic center over carbonyl carbon of the reagent

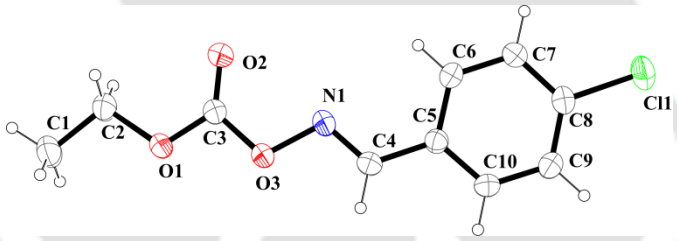
IIIa to produce *O*-ethoxycarbonyl aldoxime as intermediate **B** along with the corresponding sulphonic acid. The second equiv of the base deprotonates the hydrogen on the ethylene carbon of the imine and generates nitrile. Such participation of the Oxyma derived product in the reaction mechanism has not been described before. The intermediates **A** and **B** were purified and characterized by ^{1}H NMR, ^{13}C NMR, (*Figure S1-S4*) and ESI-MS. The intermediate **B** was further analyzed by single crystal XRD (*Figure 5.2.1a*). However, the possibility of generation of the product by intra-molecular hydrogen abstraction from both of the intermediates (**A** and **B**) as shown in scheme 5.2.1 cannot be ruled out, but that should be predominant in high dilution and high temperature condition such as in gas phase reactions as it was reported for intermediate **A**.[137]



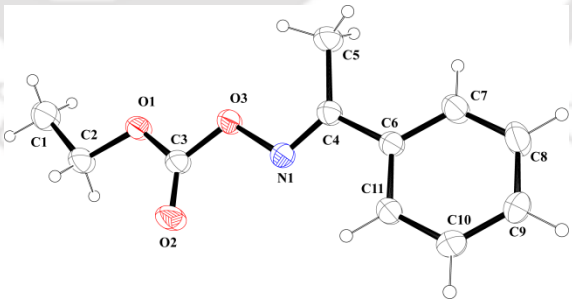
Scheme 5.2.1. Two probable pathways for the formation of nitriles by dehydration of aldoximes

In order to precisely predict the ability of DBU whether it is capable of deprotonating the ethylenic proton we have synthesized the authentic intermediates **A** and **B** with complete characterization and finally subjected to the reaction in presence and in absence of 1 equiv of DBU. Interestingly, it was found that the reaction completed in presence of DBU in 10 min, whereas it did not progress in absence of DBU (checked up to 12 h). Therefore, it can be concluded that the intra-molecular H-abstraction did not occur.

Furthermore, to support the mechanism, the reaction was repeated using a ketoxime as substrate and corresponding products to the intermediate **A** and **B** was expected. However, *O*-ethoxycarbonylketoxime (*Figure 5.2.1b*) was obtained as sole product with excellent yield. This indicates that in case of the ketoxime, either the reaction follows only path B or the first step of path A is reversible. No Oxyma could be recovered when ketoxime was used, which proves the complete involvement of Oxyma cleaved product, whereas, approximately 50% of Oxyma could be recovered when aldoxime was used as the substrate which proves that some of the cleaved product of the Oxyma is involved in the promotion of the reaction in yielding the desired nitrile quickly and with better yield than its counterpart, that is sulfonyl chlorides.[138]



(a)



(b)

Figure 5.2.1. X-ray crystallographic structure of (a) (E)-4-chlorobenzaldehyde-*O*-ethoxycarbonyl- oxime and (b) acetophenone-*O*-ethoxycarbonyloxime (ORTEP diagram with ellipsoid of 50% probability, CCDC No. 918220 and 918221 respectively)

5.3. Conclusion

In conclusion, we have demonstrated a new method for the synthesis of nitriles from aldoximes under milder conditions using *o*-NosylOXY. This method has several advantages over the existing methods as; it precludes the usage of the expensive reagents and toxic metals, long reaction times have been dropped down and heating conditions were replaced with room temperature. Therefore, the current methodology should find large applications in the synthesis of natural products where the tolerance of a good number of other functional groups is in force.

5.4. Experimental Section

5.4.1. General consideration

As described in chapter 2, section 2.6.1

5.4.2. Representative procedure for nitrile synthesis

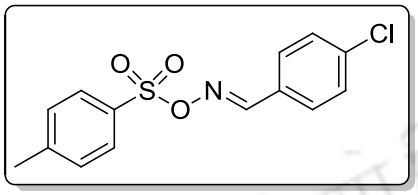
In an oven-dried two-necked 50 mL round-bottomed flask, equipped with a stirring bar, a solution of the aldoxime (1.0 mmol) and *o*-NosylOXY (1.5 mmol) dissolved in anhydrous DCM (5 mL) was placed under the atmosphere of nitrogen. The reaction mixture was stirred at room temperature for 5 min, then DBU (2.5 mmol) was added drop wise over 2 min. The reaction mixture became a clear homogeneous solution after addition of DBU. The reaction was monitored by TLC. The reaction mixture was diluted with EtOAc and washed with water (2×5 mL) followed by brine (2×5 mL) upon complete consumption of the starting material. Product was purified by column chromatography.

5.4.3. Experimental procedure followed to identify the intermediates

In an oven-dried two-necked 50 mL round-bottomed flask, equipped with a stirring bar a solution of the 4-chlorobenzaldoxime (2 mmol) and 4-CH_3-C_6H_4-SO_3XY (2.5 mmol) dissolved in anhydrous DCM (5 mL) was placed under the atmosphere of nitrogen. The mixture was stirred at room temperature for 5 min, and then TEA (2.5 mmol) was added drop wise to the stirring mixture over 2 min. The reaction mixture became a clear homogeneous solution after addition of TEA. After 30 min we observed two new spots between starting material and product in TLC. The reaction mixture was diluted with 10 mL of ethyl acetate; the organic phase was washed with 5% HCl (2×5 ml), 5% $NaHCO_3$ (2×5 ml) and dried over anhydrous Na_2SO_4. Finally, Na_2SO_4 was filtered off and the solvent was evaporated to obtain the mixture of intermediates (E)-4-chlorobenzaldehyde-*O*-tosyloxime and (E)-4-chlorobenzaldehyde-*O*-ethoxycarbonyloxime, which were purified by column chromatography. We also performed a reaction with acetophenoneoxime following the procedure as described and found acetophenone-*O*-ethoxycarbonyloxime as sole product.

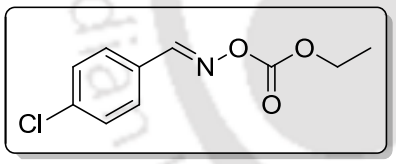
5.5. Characterization data

(*E*)-4-Chlorobenzaldehyde-*O*-tosyloxime (Intermediate A, Scheme 5.2.1)



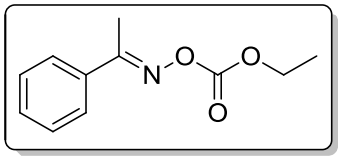
Yellow solid; R_f = 0.5 (EtOAc-Hexane, 0.5:9.5); mp: 109-111 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53 (s, 1H), 8.09-8.07 (d, *J* = 8.0 Hz, 2H), 7.75-7.72 (d, *J* = 8.2 Hz, 2H), 7.47-7.43 (m, 4H), 1.32 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.0, 155.79, 140.11, 138.10, 113.13, 129.70, 129.37, 129.03, 128.46, 126.88, 29.72 ppm; IR (KBr): 2930, 2853, 1740, 1597, 1488, 1440, 1259, 1078, 1015, 932, 820, 748, 513 cm^{-1}; LRMS = 310.0299 ($[M+H]^+$, calculated for $C_{14}H_{12}ClNO_3S$); observed = 310.3143 $[M+H]^+$.

(E)-4-Chlorobenzaldehyde-*O*-ethoxycarbonyloxime (Intermediate B, Scheme 5.2.1)



Colorless crystalline solid; R_f = 0.5 (EtOAc-Hexane, 0.6:9.4); mp: 82-83 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (s, 1H), 7.65-7.63 (d, *J* = 8.0 Hz, 2H), 7.38-7.36 (d, *J* = 8.2 Hz, 2H), 4.35-4.30 (q, 2H), 1.37-1.38 ppm (t, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.5, 153.9, 134.7, 130.6, 128.6, 127.1, 64.73 14.3 ppm; IR (KBr): 2930, 2915, 1775, 1593, 1487, 1403, 1372, 1339, 1235, 1088, 970, 947, 853, 775 cm^{-1}; LRMS (m/z) = 250.0310 ($[M+Na]^+$, calculated for $C_{11}H_{13}NO_3$); observed = 250.1043 $[M+Na]^+$.

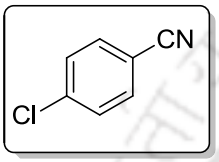
(E)-Acetophenone-*O*-ethoxycarbonyloxime (Figure 5.2.1b)



Colorless crystalline solid; R_f = 0.5 (EtOAc-Hexane, 0.6:9.4); mp: 51-53 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72-7.70 (d, *J* = 8.0 Hz, 2H), 7.41-7.37 (m, 3H), 4.35-4.29

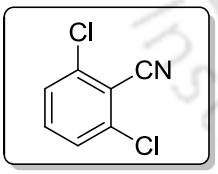
(q, 2H), 2.36 (s, 3H), 1.37-1.34 ppm (t, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.8, 153.9, 133.8, 130.7, 128.5, 127.1, 64.5, 14.3, 12.2 ppm; IR (KBr): 2983, 2963, 2929, 2907, 1765, 1371, 1309, 1242, 1008, 980, 937, 980, 861, 694, 631 cm^{-1}; LRMS = 230.0788 ($[M+Na]^+$, calculated for $C_{11}H_{13}NO_3$); observed = 230.0481 $[M+Na]^+$

4-Chlorobenzonitrile[139] (entry 1, Table 5.1.2)



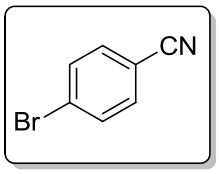
Yield: 127 mg (93%), yellowish solid; R_f = 0.5 (EtOAc/Hexane, 0.5:9.5); mp: 90-92 ^oC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58-7.56 (d, *J* = 8.4 Hz, 2H), 7.44-7.42 ppm (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.7, 133.5, 129.8, 118.1, 110.9 ppm; IR (KBr): 2924, 2853, 2224, 1715, 1593, 1541, 1398, 1261, 1088, 1016, 544 cm^{-1}; GCMS (m/z) = 137 [M^+, calculated for $C_7H_3Cl_2N$]; observed: 139, 137, 102, 76, 75, 51.

2,6-Dichlorobenzonitrile (entry 2, Table 5.1.2)



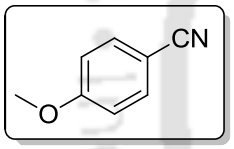
Yield: 160 mg (94%), white powder; R_f = 0.5 (EtOAc/Hexane, 0.5:9.5); mp:142-143 ^oC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48-7.38 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.5, 134.1, 128.3, 114.4, 113.5 ppm; IR (KBr): 3092, 2928, 2232, 1572, 1558, 1432, 1199, 1098, 802, 784, 713 cm^{-1}; GCMS (m/z) = 171 [M^+, calculated for $C_7H_3Cl_2N$]; observed: 173, 172, 171, 136, 100, 99, 86, 75, 50.

4-Bromobenzonitrile[140] (entry 3, Table 5.1.2)



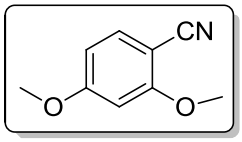
Yield: 166 mg (92%), white solid; R_f =0.5 (EtOAc/Hexane, 0.5:9.5); mp: 110-112 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62-7.60 (d, *J* = 8.4 Hz, 2H), 7.51-7.48 ppm (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 133.5, 132.7, 128.1, 118.1, 111.3 ppm; IR (KBr): 2928, 2859, 2234, 1719, 1597, 1542, 1391, 1263, 1084, 1012, 665, 541 cm^{-1}; GCMS (m/z) = 181 [M^+, calculated C_7H_3BrN], observed: 182, 181, 103, 102, 99, 6, 75 74, 73, 61, 51.

4-Methoxybenzonitrile[139] (entry 4, Table 5.1.2)



Yield: 109 mg (82%), colourless solid; R_f = 0.5 (EtOAc/Hexane, 1.0:9.0); mp: 57-59 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57-7.54 (d, *J* = 7.8 Hz, 2H), 6.94-6.91 (d, *J* = 8.0 Hz, 2H), 3.83 ppm (s, 3H) ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.9, 133.92 119.22 114.8, 103.8, 55.5 ppm; IR (KBr): 2932, 2804, 2218, 1606, 1510, 1305, 1258, 1175, 1023, 829, 681, 546 cm^{-1}; GCMS (m/z) = 133 [M^+, calculated for C_8H_7NO], observed: 133, 118, 104, 103, 90, 78, 76, 64, 63, 51, 50.

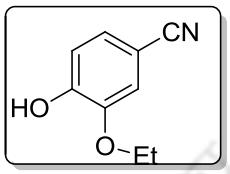
2,4-Dimethoxybenzonitrile[139] (entry 5, Table 5.1.2)



Yield: 141 mg (87%), white solid; R_f = 0.5 (EtOAc/Hexane, 1.0:9.0); mp: 59-61 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22-7.20 (m, 2H), 6.84 (s, 1H), 3.86 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.0, 149.4, 126.6, 119.1,114.1, 111.4, 104.0, 56.3 ppm; IR (KBr): 3085, 2971, 2817, 2223, 1598, 1584, 1515, 1463, 1271, 1029, 927, 811, 764, 616 cm^{-1}; GCMS

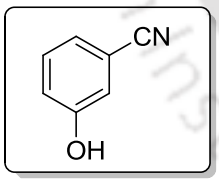
(m/z) = 163 [M^+, calculated for $C_9H_9NO_2$]; observed: 163, 148, 120, 102, 92, 77, 65, 63, 51.

3-Ethoxy-4-hydroxybenzonitrile (entry 6, Table 5.1.2)



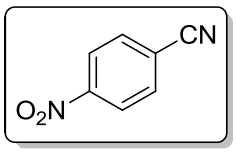
Yield: 128 mg (79%), yellowish semisolid; R_f = 0.5 (EtOAc/Hexane, 0.5:9.5); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21-7.17 (m, 1H), 7.04 (s, 1H), 6.96-6.92 (m, 1H), 6.2 (broad, 1H), 4.14-4.08 (q, *J* = 3.6 Hz, 2H), 1..47-1.45 ppm (t, *J* = 4.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.2, 149.5, 127.0, 115.4, 114.7, 65.2, 14.8 ppm; IR (KBr): 2923, 2232, 1590, 1514, 1428, 1286, 1196, 1038, 800, 532 cm^{-1}; G CMS (m/z) = 163 [M^+, calculated for $C_9H_9NO_2$]; observed: 163, 136, 105, 89, 79, 76, 63, 52, 51.

3-Hydroxybenzonitrile[138] (entry 7, Table 5.1.2)



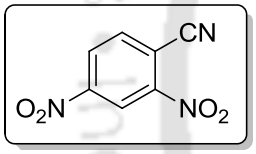
Yield: 91 mg (77%), colourless solid; R_f = 0.5 (EtOAc/Hexane, 2.0:8.0); mp: 71-73 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31-7.24 (m, 1H), 7.20-7.18 (m, 1H), 7.11-7.08 (m, 2H), 6.21 ppm (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.7, 130.8, 124.5, 121.1, 118.9, 112.7 ppm; IR (KBr): 2932, 2235, 1635, 1536, 1481, 378, 1353, 1353, 1189, 1189, 1125, 934, 809, 796, 731, 677, 587, 546 cm^{-1}; GCMS (m/z) = 119 [M^+, calculated for C_7H_5NO]; observed: 119, 118, 91, 76, 64, 63, 52, 51, 50.

4-Nitrobenzonitrile[140] (entry 8, Table 5.1.2)



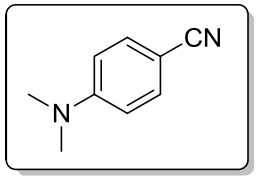
Yield: 131 mg (89%); yellowish solid; R_f = 0.5 (EtOAc/Hexane, 1.5:8.5); mp: 141-145 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32-8.30 (d, *J* = 8.4 Hz, 2H), 7.88-7.86 ppm (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.12, 133.62, 124.37, 118.37,116.94 ppm; IR (KBr): 2926, 2851, 2214, 1717, 1593, 1398, 1261, 1088, 1016, 668, cm^{-1}; GCMS (m/z) = 148 [M^+, calculated for $C_7H_4N_2O_2$], 148, 118, 102, 90, 75, 63, 51.

2,4-Dinitrobenzonitrile (entry 9, Table 5.1.2)



Yield: 167 mg (87%), white solid, R_f = 0.5 (EtOAc/Hexane, 1.5:8.5); mp 102-103 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$):δ 9.12 (s, 1H), 8.67-8.64 (d, *J* = 8.0 Hz, 1H), 8.20-8.17 ppm (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.2, 149.1, 137.3, 128.7, 121.1, 113.4, 113.3 ppm; IR (KBr): 2932, 2235, 1635, 1536, 1481, 378, 1353, 1353, 1189, 1189, 1125, 934, 809, 796, 731, 677, 587, 546 cm^{-1}; GCMS (m/z) = 193 [M^+, calculated for $C_7H_3N_3O_4$]; observed: 193, 147, 117, 101, 100, 91, 89, 75, 62, 50.

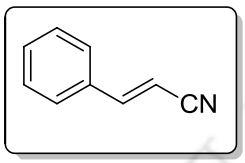
4-(Dimethylamino)benzonitrile[139] (entry 10, Table 5.1.2)



Yield: 113 mg (78%), white solid; R_f = 0.5 (EtOAc/Hexane, 2.0:8.0); mp: 71-73 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.38 (d, *J* = 7.8 Hz, 2H), 6.60-6.58 (d, *J* = 8.0 Hz, 2H), 2.99 ppm (s, 6H) ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.3, 133.1, 120.6, 111.3, 96.9, 39.7 ppm; IR (KBr): 2934, 2818, 2211, 1607, 1525, 1448, 1371, 1225, 1178, 1122, 941, 818 cm^{-1};

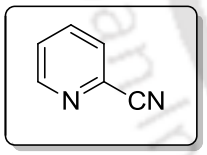
GCMS (m/z) = 146 [M^+, calculated for $C_9H_{10}N_2$]; observed: 146, 145, 130, 129, 116, 102, 77, 75, 64, 51.

Cinnamonitrile[141] (entry 11, Table 5.1.2)



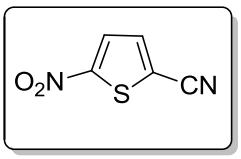
Yield: 110 mg (86%), liquid; R_f = 0.5 (EtOAc/Hexane, 1.0:9.0); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.27 (m, 6H), 5.89-5.85 ppm (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.5, 133.5, 131.2, 129.1, 127.4, 118.2, 96.3 ppm; IR (KBr): 2923, 2851, 2214, 1621, 1437, 1262, 1127, 748, 688, 507cm^{-1}; GCMS (m/z) = 129 [M^+, calculated for $C_7H_3Cl_2N$]; observed: 129, 128, 103, 102, 83, 76, 64, 51.

2-Cyanopyridine[142] (entry 12, Table 5.1.2)



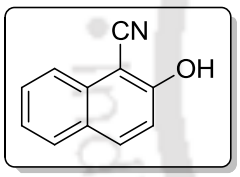
Yield: 88 mg (85%), liquid; R_f = 0.5 (EtOAc/Hexane, 2.0:8.0); ^{1}HNMR (400 MHz, $CDCl_3$): δ 8.75-8.73 (d, *J* = 8.0 Hz, 1H), 7.88-7.84 (m, 1H),7.73-7.71 (d, *J* = 8.0 Hz, 1H), 7.56-7.53 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.3, 137.3, 134.1, 128.7, 127.1, 117.3 ppm; IR (KBr): 2923, 2813, 2236, 1625, 1681, 1462, 1154, 992, 781, 737, 551 cm^{-1}; GCMS (m/z) = 104 [M^+, calculated for $C_6H_4N_2$]; observed: 104, 78, 76, 75, 51.

5-Nitrothiophene-2-carbonitrile[143] (entry 13, Table 5.1.2)



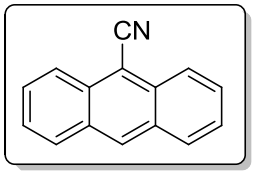
Yield: 127 mg (83%), liquid; R_f = 0.5 (EtOAc/Hexane, 1.0:9.0); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88-7.86 (d, *J* = 8.0 Hz, 1H), 7.58-7.56 ppm (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.6, 136.7, 127.8, 115.4, 112.1 ppm; IR (KBr): 3114, 2930, 2823, 2226, 1626, 1537, 1426, 1350, 1335, 1129, 1119, 981, 730, 567, 512 cm^{-1}; GCMS (m/z) = 154 [M^+, calculated for $C_5H_2N_2O_2S$]; observed: 154, 124, 108, 96, 81, 70, 64, 56.

2-Hydroxy-1-naphthonitrile[144] (entry 14, Table 5.1.2)



Yield: 133 mg (79%), liquid; R_f = 0.5 (EtOAc/Hexane, 2.0:8.0); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98-7.96 (d, *J* = 8.0 Hz, 1H), 7.89-7.85 (m, 1H), 7.80-7.71 (m, 2H), 7.62-7.55 (m, 1H), 7.15-7.13 ppm (d, *J* = 8.2, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.3, 132.6, 129.4, 129.3, 127.4, 125.8, 125.2, 125.1, 124.4, 123.9, 117.9 ppm; IR (KBr): 2934, 2853, 2257, 1715, 1646, 1583, 1541, 1358, 1261, 1088, 1036, 678 cm^{-1}; GCMS (m/z) = 169 [M^+, calculated for $C_{11}H_7NO$]; observed: 169, 154, 124, 108, 96, 81, 70, 64, 56.

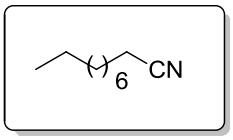
Anthracene-10-carbonitrile[145] (entry 15, Table 5.1.2)



Yield: 164 mg (81%), yellow solid; R_f = 0.5 (EtOAc/Hexane, 1.0:9.0); mp: 174-177 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.62 (s, 1H), 8.37-8.34 (d, *J* = 8.2 Hz, 2H), 8.02-8.00 (d, *J* = 8.0 Hz, 2H), 7.67-7.65 (m, 2H), 7.56-7.54 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 133.5 132.9, 130.8, 129.1, 126.5, 125.5 ppm; IR (KBr): 2930, 2853, 2213, 1624, 1444, 1262, 1018,

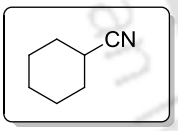
898, 846, 730, 583, 563, 563, 538 cm^{-1}; GCMS (m/z) = 203 [M^+, calculated for $C_{15}H_9N$]; observed: 203, 202, 176, 102, 88.

Decanenitrile (entry 16, Table 5.1.2)



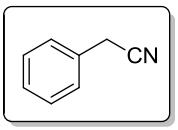
Yield: 124 mg (82%), oil liquid; R_f = 0.5 (EtOAc/Hexane, 1.0:9.0); ^1H NMR (400 MHz, $CDCl_3$): δ 2.30-2.27 (t, 2H), 1.64-1.57 (m, 2H), 1.41-1.36 (m, 2H), 1.29-1.22 (m, 10H), 0.85-0.82 ppm (t, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 119.8, 31.8, 29.3, 29.2, 28.7, 28.6, 25.4, 22.6, 17.1, 14.1 ppm; IR (KBr): 2927, 2856, 2247, 1748, 1466, 1377, 1260, 1116, 718 cm^{-1}; LRMS (m/z) = 176.14 ([M+Na]$^+$, calculated for $C_{10}H_{19}N$); observed = 176.18 [M+Na]$^+$.

Cyclohexanecarbonitrile (entry 17, Table 5.1.2)



Yield: 82 mg (76%), oil liquid; R_f = 0.5 (EtOAc/Hexane, 1.0:9.0); ^1H NMR (400 MHz, $CDCl_3$): δ 2.59-2.55 (m, 1H), 1.79-1.76 (m, 2H), 1.68-1.62 (m, 4H), 1.46-1.36 ppm (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 122.7, 29.5, 28.0, 25.3, 24.1 ppm; IR (KBr): 2930, 2878, 2236, 1627, 1451, 1259, 725 cm^{-1}; LRMS (m/z) = 110.0964 ([M+H]$^+$, calculated for $C_7H_{11}N$); observed = 110.167 [M+H]$^+$.

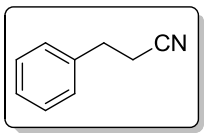
2-Phenylacetonitrile (entry 18, Table 5.1.2)



Yield: 86 mg (74%), oil liquid; R_f = 0.5 (EtOAc/Hexane, 0.5:9.5); ^1H NMR (400 MHz, $CDCl_3$): δ 7.36-7.34 (m, 2H), 7.32-7.29 (m, 3H); 3.72 ppm (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 130.1, 129.3, 128.6, 128.1, 118.0, 23.1

ppm; IR (KBr): 2918, 2850, 2251, 1603, 1521, 1416, 1028, 735, 696 cm^{-1}; LRMS (m/z) = 118.0651 ($[M+H]^+$, calculated for C_8H_7N); observed = 118.0763 $[M+H]^+$.

3-Phenylpropanenitrile (entry 19, Table 5.1.2)



Yield: 102 mg (78%), oil liquid; R_f = 0.5 (EtOAc/Hexane, 0.5:9.5); ^1H NMR (400 MHz, $CDCl_3$): δ 7.33-7.30 (m, 2H), 7.27-7.25 (m, 1H), 7.21-7.20 (m, 2H), 2.92-2.89 (t, 2H), 2.58-2.54 ppm (t, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.2, 128.8, 128.3, 127.2, 119.2, 31.5, 19.3 ppm; IR (KBr): 2928, 2851, 2223, 1634, 1445, 1016, 730, 583, 553 cm^{-1}; LRMS (m/z) = 132.0808 ($[M+H]^+$, calculated for C_9H_9N); observed = 132.0951 $[M+H]^+$.

5.6 Selected spectra

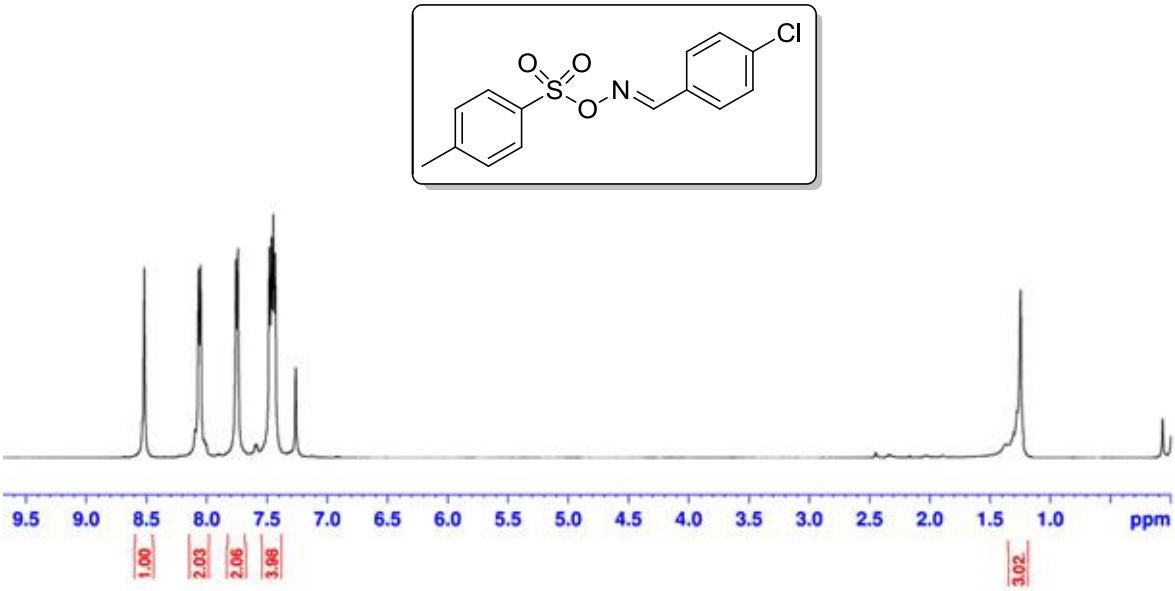


Figure S1: ^{1}H-NMR spectrum of (E)-4-chlorobenzaldehyde-O-tosyloxime (Intermediate A, Scheme 5.2.1)

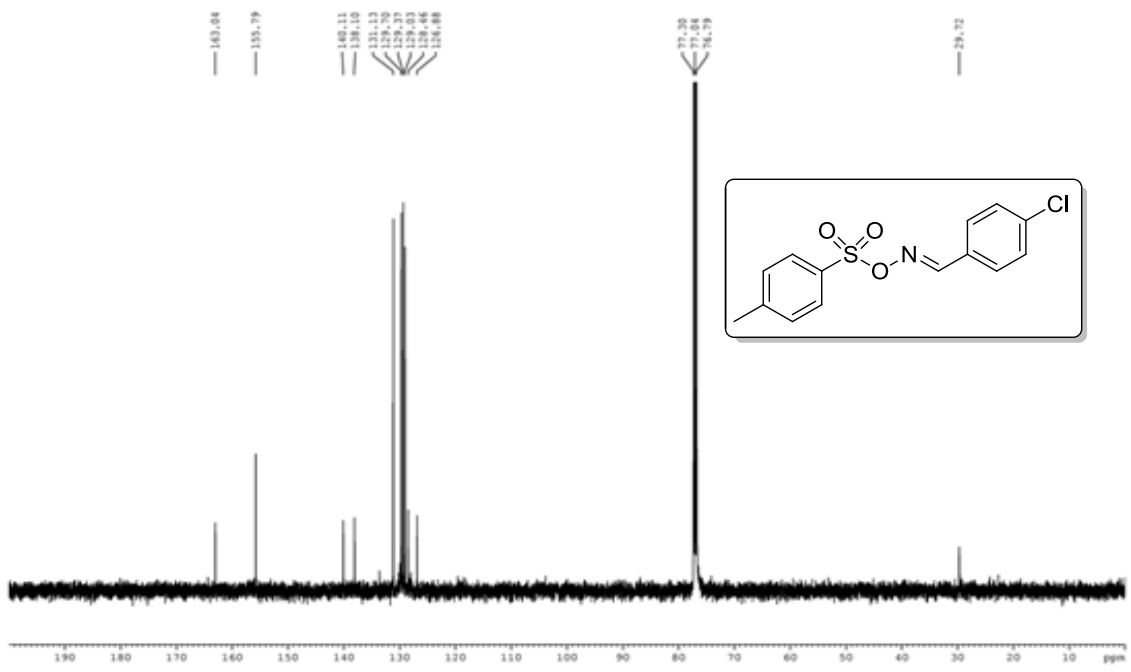


Figure S2: ^{13}C-NMR spectrum of (E)-4-chlorobenzaldehyde-*O*-tosyloxime (Intermediate A, Scheme 5.2.1)

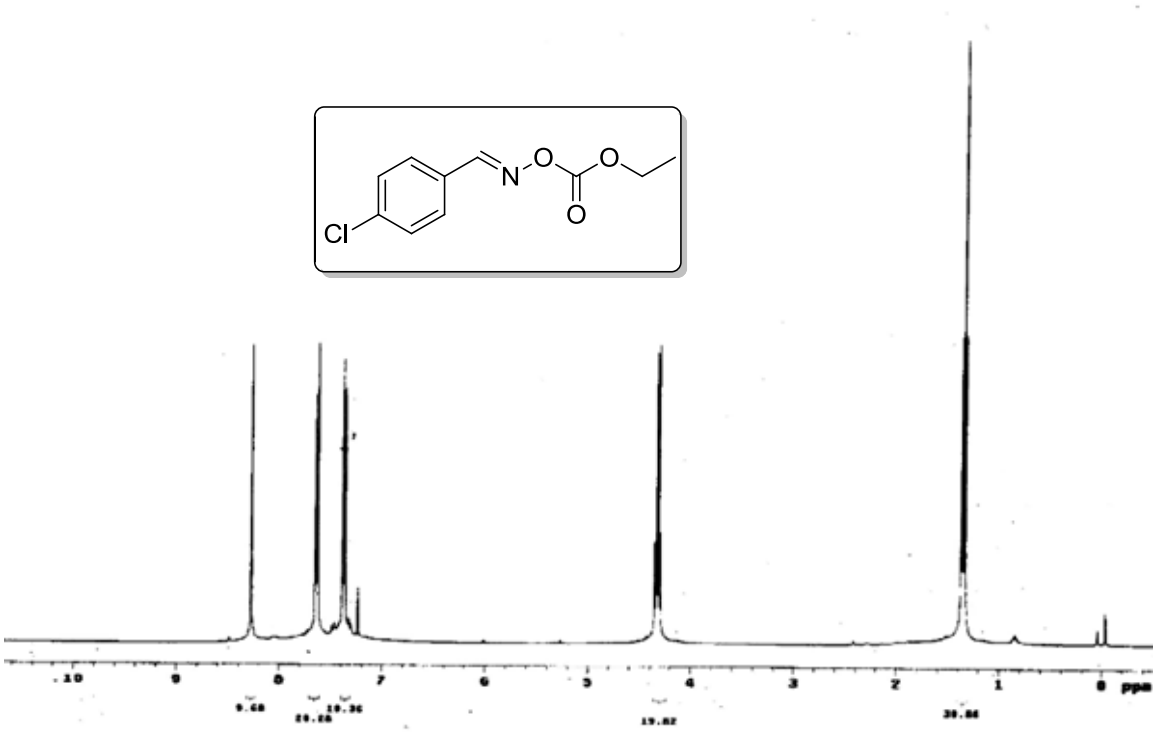


Figure S3: ^{1}H-NMR spectrum of (E)-4-chlorobenzaldehyde *O*-ethoxycarbonyloxime (Intermediate B, Scheme 5.2.1)

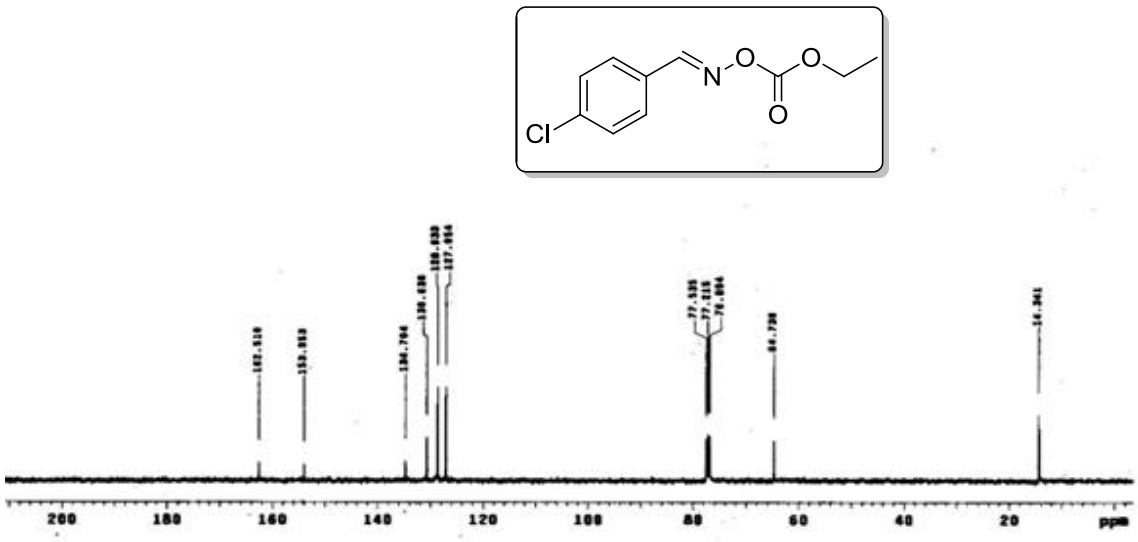


Figure S4: ^{13}C-NMR spectrum of (E)-4-chlorobenzaldehyde *O*-ethoxycarbonyloxime (Intermediate B, Scheme 5.2.1)

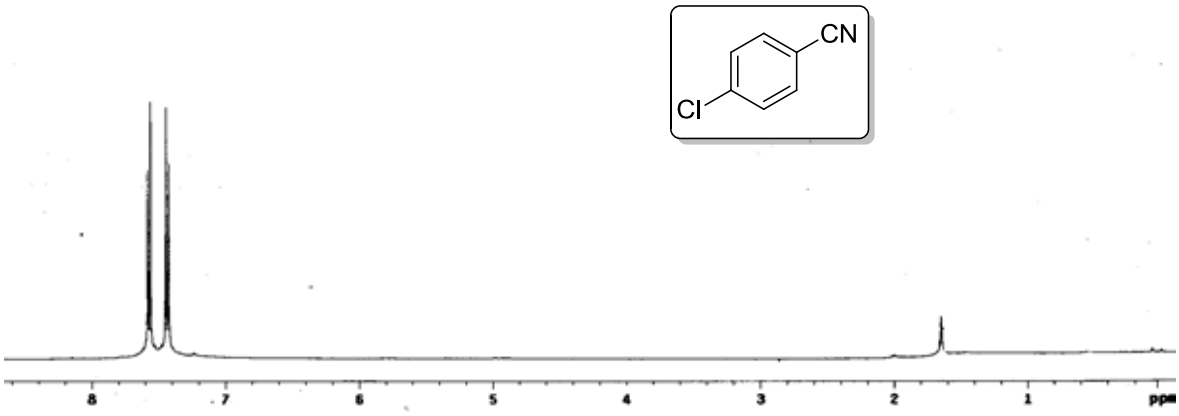


Figure S5: [1] H-NMR spectrum of 4-chlorobenzonitrile (entry 1, Table 5.1.2)

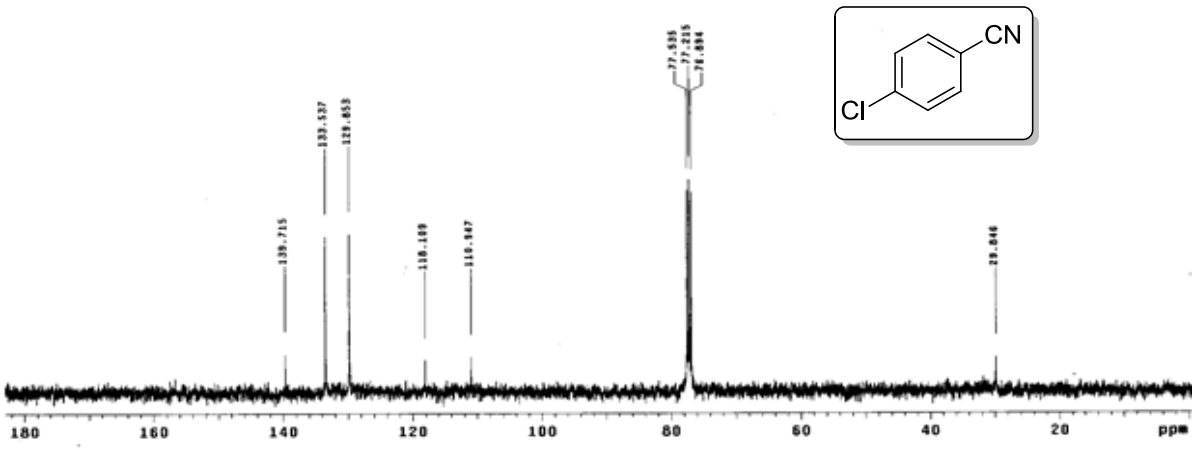


Figure S6: [13]C-NMR spectrum of 4-chlorobenzonitrile (entry 1, Table 5.1.2)

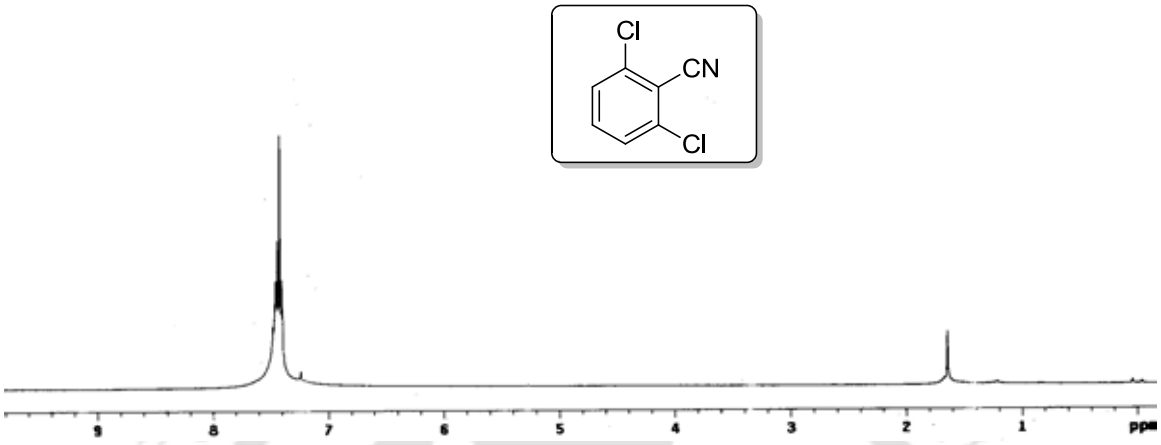


Figure S7: [1]H-NMR spectrum of 2,6-dichlorobenzonitrile (entry 2, Table 5.1.2)

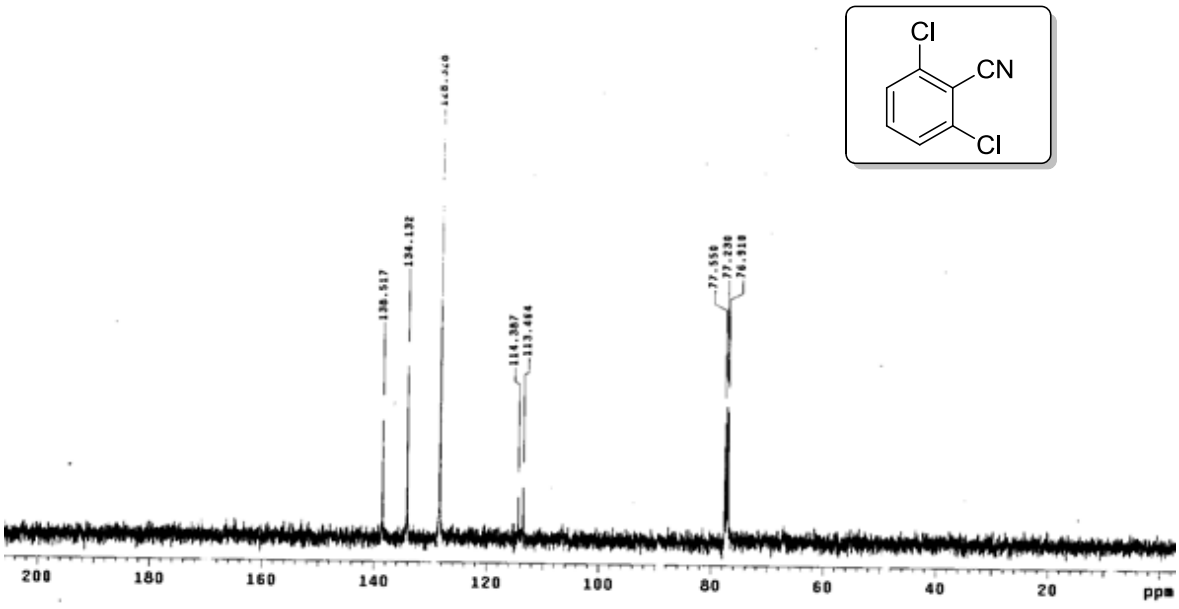


Figure S8: [13]C-NMR spectrum of 2,6-dichlorobenzonitrile (entry 2, Table 5.1.2)

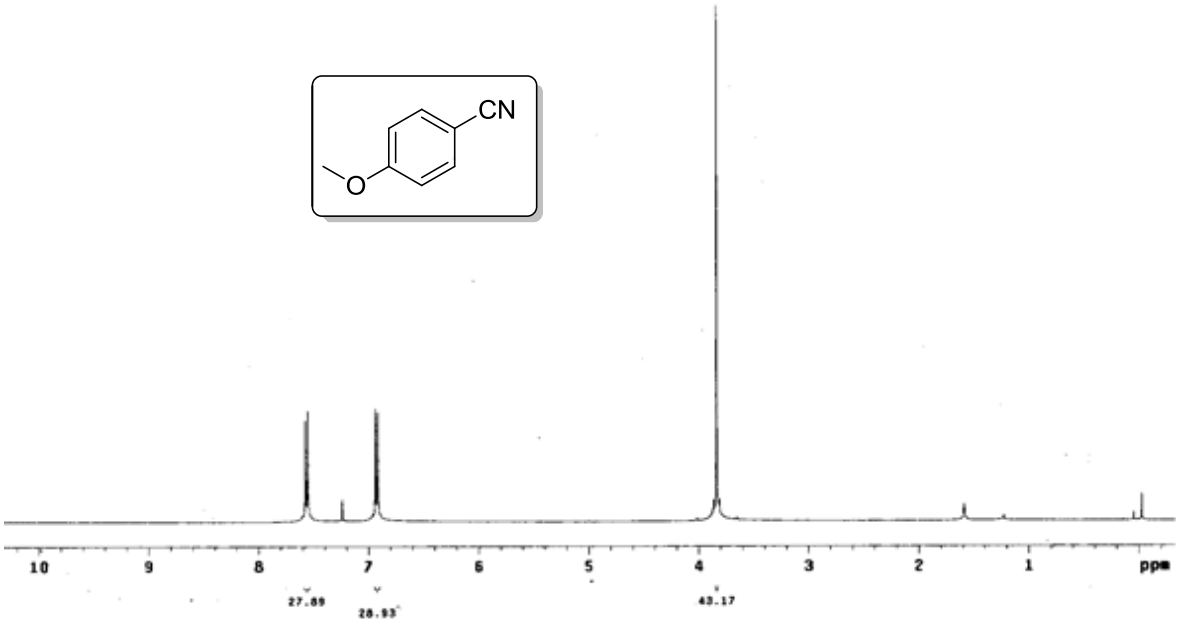


Figure S9: ^{1}H-NMRspectrum of 4-methoxybenzonitrile (entry 4, Table 5.1.2)

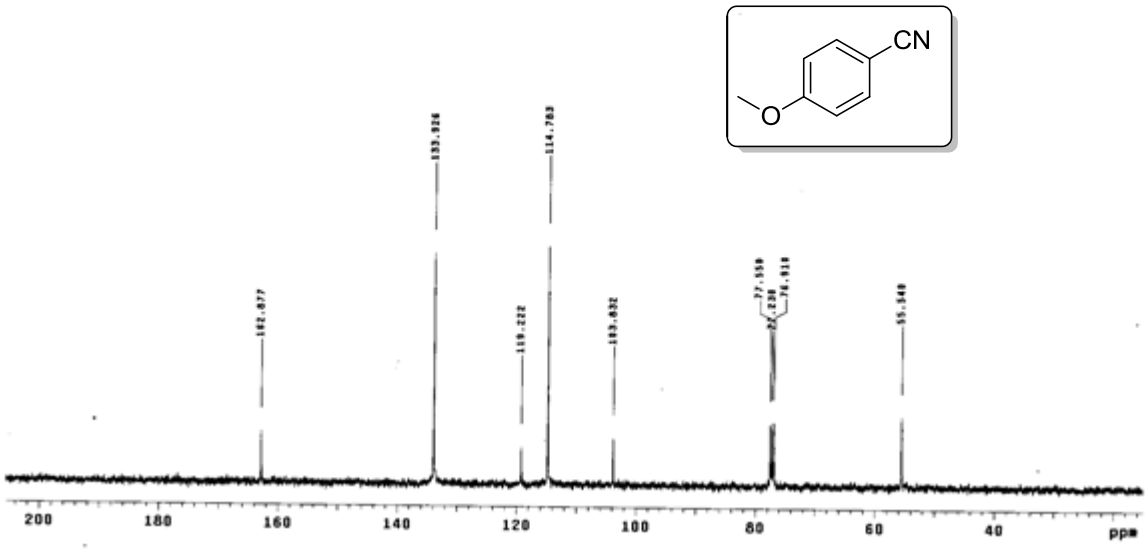
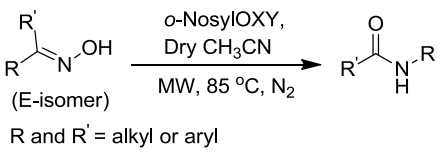


Figure S10: ^{13}C-NMR spectrum of 4-methoxybenzonitrile (entry 4, Table 5.1.2)

Chapter 6: Synthesis of Amide from Ketoxime via Beckmann Rearrangement using Catalytic amount of Ethyl 2-cyano-2-(2-nitrobenzenesulfonyloxyimino) acetate (*o*-NosylOXY)

After successfully demonstration of the reagent *o*-NosylOXY for the synthesis of amide, peptides, esters, hydroxamates, benzoxazoles, benzothiazoles and nitriles, we further want to explore the application of *o*-NosylOXY for the synthesis of amide and ε-lactam from ketoxime via Beckmann rearrangement (BKR). The synthesis of amides via Beckmann rearrangement (BKR) is one of the well-known methods in organic chemistry which included the synthesis of ε-lactams from cyclic ketoximes. There are several literatures available for synthesis of amide and ε-lactam via BKR (Chapter 1, section 1.8); most of these methods suffered from some drawbacks, including the use of strong acids and metals. Herein, we demonstrate the synthesis of amide from ketoxime using organocatalyst *o*-NosylOXY (*Scheme 6.1*).

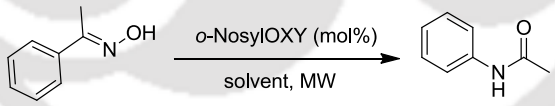


Scheme 6.1. Synthesis of amide from ketoxime

6.1. Synthesis of amides via Beckmann rearrangement using *o*-NosylOXY

The preparation of *o*-NosylOXY was shown in chapter 2, section 2.1.1. For a model reaction, we have taken acetophenone oxime (1 equiv) and *o*-NosylOXY (1 equiv) dissolved in dry acetonitrile and the reaction kept under microwave at 85 ^{o}C for 30 min. The reaction was monitored by TLC. After completion of the reaction 97% yield was obtained. For optimization, we screened various solvents, including toluene, tetrahydrofuran, chloroform, ethyl acetate, dichloromethane, acetonitrile and 1,4-dioxane, we observed acetonitrile as the best solvent for the reaction under optimized condition. We did not observed any trace of product, when dichloromethane or 1,4-dioxane was used as solvent. After optimization of the solvent, we checked the catalytic activity of the reagent *o*-NosylOXY with different mol% of it (*entry 1 to 5*, *Table 6.1.1*). We observed 5 mol% of the reagent was sufficient for the reaction with excellent yield (97%).

Table 6.1.1. Optimization of the reaction conditions[a]

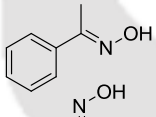
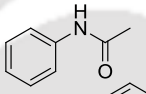
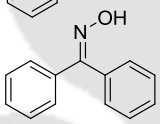
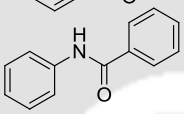
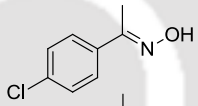
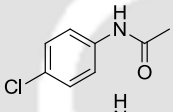
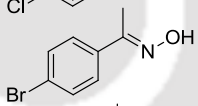
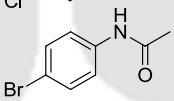
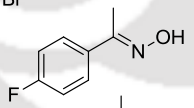
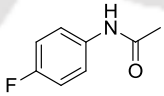
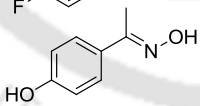
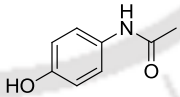
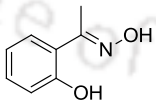
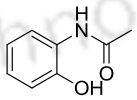
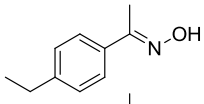
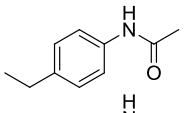
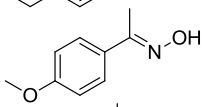
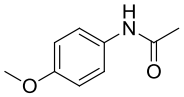
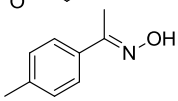
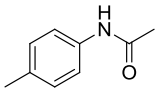
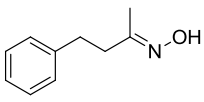
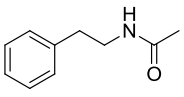


Entry[a]	Solvent	*o*-NosylOXY (mol %)	Time (min.)	Yield (%)[b]
1.	Acetonitrile	100	10	97
2.	Acetonitrile	75	10	96
3.	Acetonitrile	50	10	97
4.	Acetonitrile	10	10	98
5.	Acetonitrile	5	10	97
6.	Acetonitrile	0	10	NR
7.	DCM	5	30	NR
8.	Toluene	5	30	30
9.	1,4-dioxane	5	40	NR
10.	THF	5	30	20
11.	EtOAc	5	30	10
12.	$CHCl_3$	5	40	30

[a]Performed with acetophenone oxime (1 equiv) and o-NosylOXY (mol%) MW at 85 ºC under N_2. [b]Yields refer to the isolated yield after column chromatography.

After optimizing the conditions, we went to explore the substrate scope of the methodology. The reaction worked well with electron donating and withdrawing groups containing ketoxime, including chloro, bromo, fluoro (*entry 3-5, Table 6.1.2*), hydro (*entry 6 & 7, Table 6.1.2*) and methoxy (*entry 9, Table 6.1.2*) and observed most of them produced excellent yield. Cyclohexanone oxime and cycloheptanone oxime were also produced in good yield (*entries 13-14, Table 6.1.2*).

Table:6.1.2. Synthesis of various amides[a]

Entry	Ketoxime	Amide	Yield (%)[b]
1			96
2			94
3			95
4			94
5			94
6			90
7			88
8			89
9			87
10			87
11			85

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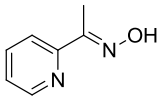
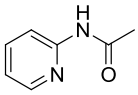
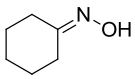
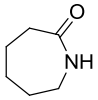
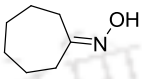
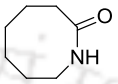
12			80
13			69
14			71

[a]*Performed with ketoxime (1 equiv) and Reagent* ***I*** *(5 mol%) under MW at 85 °C under* N_2. [b]*Yields refer to the isolated yield after column chromatography.*

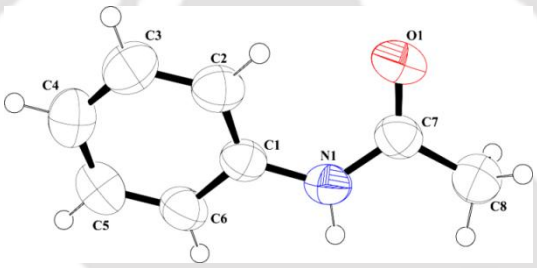
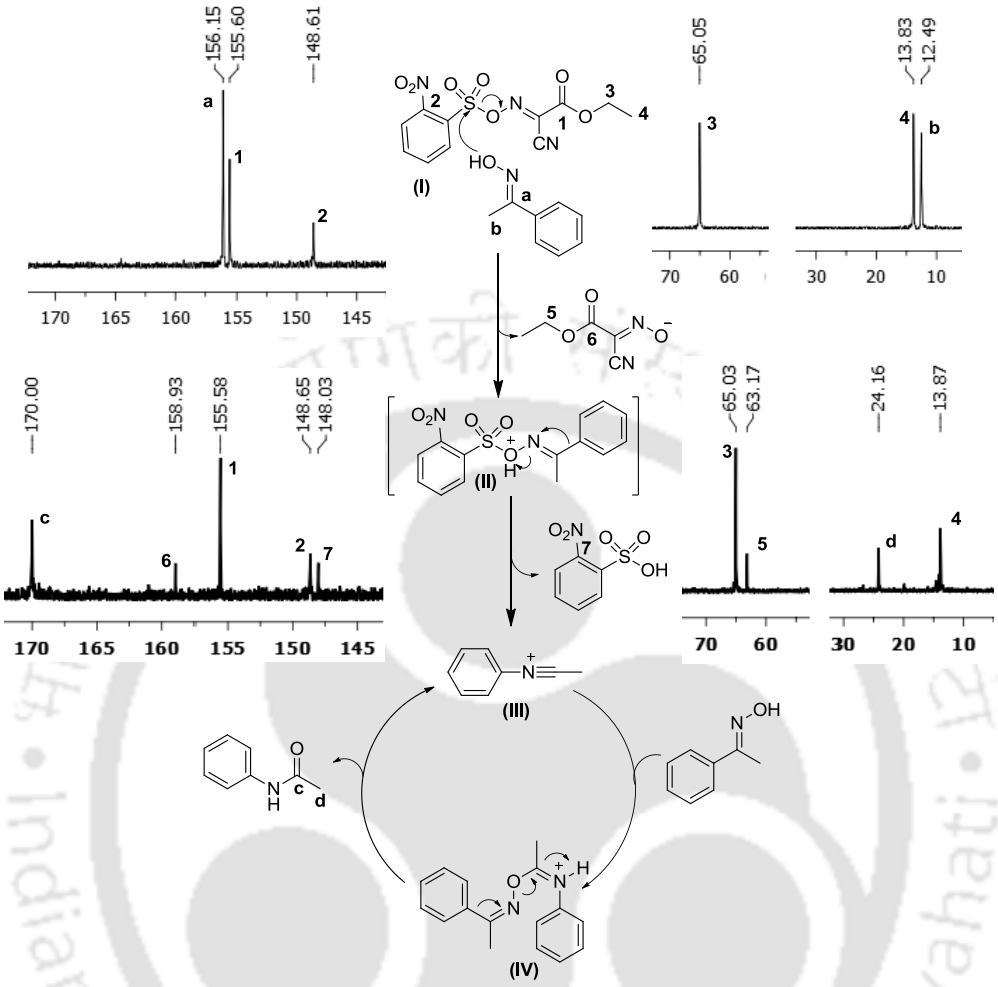


Figure 6.1.1. X-ray crystallographic structure of the product (entry 1, Table 6.1.2) (ORTEP diagram with ellipsoid of 30% probability, CCDC No. 1487430).

6.2. Plausible Mechanism

A plausible mechanism is depicted in scheme 6.2.1. At the initialization step, one molecule of ketoxime attacks the electrophilic center of **I** with the generation of Oxyma and the cationic intermediate (**II**). The Intermediate (**II**) undergoes aryl migration to generate the nitrilium cation (**III**) which was characterized by HRMS (*Figure S15*). Then, second molecule of acetoxime attacks the nitrilium cationic species (**III**) to form a dimeric species (**IV**), followed by the trans-migration of the R group (**IV**) via Beckmann rearrangement to produce the desired product and the nitrilium cation (**III**). The reaction continues in a cyclic fashion till the complete consumption of the nitrilium cation (**III**) and the substrate. To demonstrate the proposed mechanism, we performed time

dependent ^{1}H NMR and ^{13}C NMR (*Figure S16-S23*) experiments with 1 equiv of acetophenone oxime and 0.5 equivalent of *o*-NosylOXY in $CDCl_3$ as solvent under reflux condition (not under microwave) to slow down the reaction. In ^{13}C NMR, at 0 min, the peak **1** corresponds to the carbonyl (CO) carbon at 155.6, **2** corresponds to the nitro group attached carbon at 148.6, and **3**, **4**, correspond to the ethyl carbon and the methyl carbon at 65.0, 13.8 of the reagent **I** (*Figure S17*), respectively. Similarly at 0 min, peak **a** corresponds to the carbonyl carbon (CO) at 156.1 and **b** corresponds to the methyl carbon at 12.4 of acephenone oxime (*Figure S17*). We performed ^{13}C NMR at 10, 20, 30 and 40 min intervals; however did not observe any significant change (*Figure S24-S25*). From 50 to 135 min onwards significant changes were observed, two new peaks started to appear, the first peak **c** corresponds to the carbonyl (CO) at 170.0 (*Figure S26*) and the second peak **d** corresponds to the methyl carbon at 24.2 (*Figure S27*) of the desired product, *N*-phenylacetamide. At 135 min, there were two new peaks **5, 6** which corresponded to the free Oxyma and the peak **7** denoted 2-nitro substituted carbon of the free 2-nitrosulfonic acid. Interestingly, the peaks **1**, **2, 3** and **4** persisted in the spectra throughout the reaction indicating that the reagent **I** was not consumed completely. This clearly indicated either only catalytic amount of **I** was needed for the reaction or **I** was working as an initiator for the reaction. However, the presence of the slight amount of nitrobenzene sulfonic acid and Oxyma indicates that most probably **I** was working as an initiator for the reaction not in a catalytic fashion. Eriksson and co-workers[146] also proved a similar mechanism theoretically using DFT calculation in presence of other organocatalysts, including TsCl, BOP-Cl, *etc.*



Scheme 6.2.1. Plausible mechanism for the synthesis of amide from ketoxime via Beckmann rearrangement

6.3. Conclusion

We have developed a new highly effective organocatalyst for the synthesis of amides/lactams via Beckmann rearrangement from the corresponding ketoximes with good yields. This is broadening the scope of catalytic Beckmann rearrangement. A rigorous mechanistic investigation is carried out. For the synthesis of nitrile, Table 5.1.2 stereochemistry did not matter for the reaction whereas the synthesis of amide, Table 6.1.2 via Beckmann rearrangement is a stereospecific trans (stereospecific reaction of oximes) shift, otherwise reaction will not proceed.

6.4. Experimental section

2.4.1. General consideration

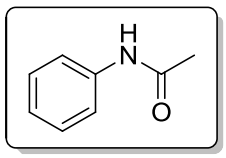
As described in chapter 2, section 2.6.1.

2.4.2. General procedure for synthesis of amide and lactam

Ketoxime (1 mmol) and *o*-NosylOXY (5 mol%) were dissolved in 5 mL of dry acetonitrile under nitrogen and the reaction mixture was reflux under microwave for 10-20 min. The progress of the reaction was monitored by TLC. After completion of the reaction, acetonitrile was evaporated by rotavapour and the reaction mixture was diluted by 5 mL of ethyl acetate followed by 3 times washing with 5% aqueous $NaHCO_3$ solution. Finally, the organic layer was dried with Na_2SO_4 and product was purified by column chromatography.

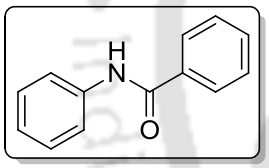
6.5. Characterization data

N-Phenylacetamide[147] (entry 1, Table 6.1.2)



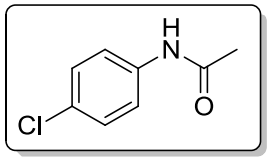
Yield: 129 mg (96%); white solid; R_f = 0.30 (EtOAc:Hexane, 3.0:7.0); mp: 112-115 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.50-7.49 (d, *J* = 7.8 Hz, 2H), 7.32-7.30 (t, *J* = 7.2 Hz, 2H), 7.12-7.09 (t, *J* = 7.2 Hz, 1H), 2.17 ppm (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 168.8, 138.1, 129.1, 124.5, 120.2, 24.7 ppm; IR (KBr): 3294, 1664, 1598, 1435, 1322, 1264, 754, 510 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_8H_{10}NO$ 136.0757, found 136.0759.

N-Phenylbenzamide[147] (entry 2, Table 6.1.2)



Yield: 185 mg (94%); white crystalline powder; R_f = 0.40 (EtOAc:Hexane, 2.5:7.5); mp: 160-163 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.93 (br, 1H), 7.87-7.86 (d, *J* = 7.2 Hz, 2H), 7.65-7.64 (d, *J* = 7.8 Hz, 2H), 7.55-7.53 (t, *J* = 7.2 Hz, 1H), 7.48-7.46 (t, *J* = 7.2 Hz, 2H), 7.38-7.36 (t, *J* = 7.8 Hz, 2H), 7.16-7.14 ppm (t, *J* = 7.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 166.0, 138.1, 135.2, 132.0, 129.3, 128.9, 127.2, 124.8, 120.4 ppm; IR (KBr): 3344, 2920, 1655, 1599, 1438, 1322, 750, 649, 583 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{13}H_{12}NO$ 198.0914, found 198.0919.

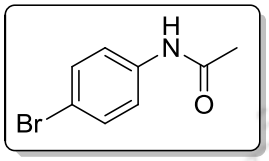
N-(4-Chlorophenyl)acetamide[148] (entry 3, Table 6.1.2)



Yield: 160 mg (95%); white solid; R_f = 0.35 (EtOAc:Hexane, 3.0:7.0); mp: 174-177 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.46-7.45 (d, *J* = 9.0 Hz, 2H), 7.28-7.27 (d, *J* = 9.0 Hz, 2H), 2.17 ppm (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 168.5, 139.5, 136.6, 129.5, 121.3, 29.9 ppm; IR

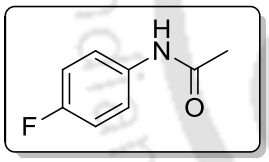
(KBr): 3297, 2922, 1662, 1601, 1489, 1261, 1091, 802, 507 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for C_8H_9ClNO 170.0368, found 170.0367.

_N_-(4-Bromophenyl)acetamide[149] (entry 4, Table 6.1.2)



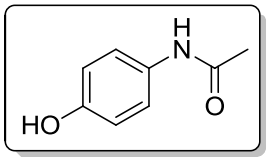
Yield: 199 mg (94%); white solid; R_f = 0.35 (EtOAc:Hexane, 3.0:7.0); mp: 167-169 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.45-7.41 (m, 4H), 2.16 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.7, 137.2, 132.1, 121.6, 117.0, 29.9 ppm; IR (KBr): 3486, 3295, 3269, 3181, 3132, 1671, 1512, 1488, 1312, 1257, 1170, 885, 655 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for C_8H_9BrNO 213.9863, found 213.9864.

_N_-(4-Fluorophenyl)acetamide[148] (entry 5, Table 6.1.2)



Yield: 144 mg (94%); white powder; R_f = 0.35 (EtOAc:Hexane, 3.0:7.0); mp: 139-141 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (br, 1H), 7.42-7.40 (d, *J* = 8.0 Hz, 2H), 6.98-6.96 (d, *J* = 8.0 Hz, 2H), 2.12 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.8, 160.8, 134.1, 122.1, 115.8, 24.5 ppm; IR (KBr): 3292, 2936, 1655, 1641, 762, 541 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for C_8H_9FNO 154.0663, found 154.066.

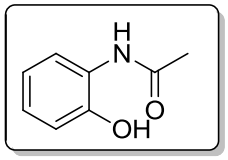
_N_-(4-Hydroxyphenyl)acetamide[150] (entry 6, Table 6.1.2)



Yield: 136 mg (90%); white crystalline solid; R_f = 0.25 (EtOAc:Hexane, 3.0:7.0); mp: 167-169 °C; ^{1}H NMR (400 MHz, $CDCl_3$ and 1 drop of CD_3OD): δ 7.22-7.20 (d, *J* = 8.0 Hz, 2H), 6.69-6.67 (d, *J* = 8.0 Hz, 2H), 4.07 (broad, OH), 2.02 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 153.6, 130.1, 122.3, 115.2, 23.3 ppm; IR (KBr): 3354, 2931, 1654,

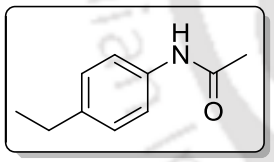
1641, 1234, 863, 541 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_8H_{10}NO_2$ 152.0707, found 152.0707.

_N_-(2-Hydroxyphenyl)acetamide[151] (entry 7, Table 6.1.2)



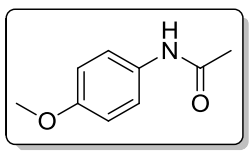
Yield: 133 mg (88%); white crystalline solid; R_f = 0.25 (EtOAc:Hexane, 3.0:7.0); mp: 207-209 °C; ^{1}H NMR (400 MHz, $CDCl_3$ and 1 drop of CD_3OD): δ 7.16-7.14 (m, 1 H), 7.02-6.98 (m, 2 H), 6.88-6.85 (m, 1 H), 4.04 (broad, OH), 2.01 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5, 152.6, 130.6, 122.1, 114.2, 24.3 ppm; IR (KBr): 3352, 2938, 1645, 1232, 861, 547 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_8H_{10}NO_2$ 152.0707, found 152.0709.

_N_-(4-Ethylphenyl)acetamide[152] (entry 8, Table 6.1.2)



Yield: 145 mg (89%); white solid; R_f = 0.35 (EtOAc:Hexane, 3.0:7.0); mp: 87-89 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.36 (d, *J* = 8.4 Hz, 2H), 7.12-7.10 (d, *J* = 8.4 Hz, 2H), 2.61-2.55 (q, 2H), 2.13 (s, 3H), 1.20-1.16 ppm (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.0, 140.5, 135.8, 128.3, 120.5, 28.4, 24.5, 15.9 ppm; IR (KBr): 3374, 2929, 1631, 1492, 1453, 1358, 1265, 1137, 1077, 948, 543 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{10}H_{14}NO$ 164.1070, found 164.1075.

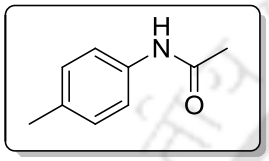
_N_-(4-Methoxyphenyl)acetamide[147] (entry 9, Table 6.1.2)



Yield: 143 mg (87%); white crystalline solid; R_f = 0.30 (EtOAc:Hexane, 3.0:7.0); mp: 126-129 °C; ^{1}H NMR (600 MHz,

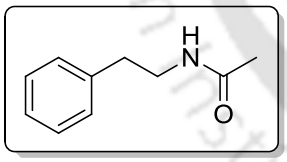
$CDCl_3$): δ 7.39-7.38 (d, *J* = 9.0 Hz, 2H), 6.86-6.84 (d, *J* = 9.0 Hz, 2H), 3.78 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 168.4, 156.7, 131.1, 122.2, 114.4, 55.7, 24.6; IR (KBr): 3302, 2923, 1655, 1564, 1134, 876, 544 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_9H_{12}NO_2$ 166.0863, found 166.0867.

_N_-(_p_-Tolyl)acetamide[147] (entry 10, Table 6.1.2)



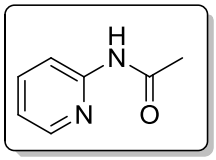
Yield: 129 mg (87%); colorless solid; R_f = 0.35 (EtOAc:Hexane, 3.0:7.0); mp: 151-153 °C; ^1H NMR (600 MHz, $CDCl_3$): δ 7.37-7.36 (d, *J* = 8.4 Hz, 2H), 7.11-7.09 (d, *J* = 8.4 Hz, 2H), 2.29 ppm (s, 3H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.0, 135.5, 134.1, 129.6, 120.4, 24.5, 21.0 ppm; IR (KBr): 3290, 2965, 1662, 1543, 1378, 1211, 820, 510 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_9H_{12}NO$ 150.0914, found 150.0918.

_N_-Phenethylacetamide[151] (entry 11, Table 6.1.2)



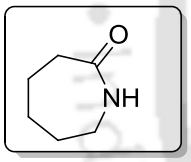
Yield: 138 mg (85%); white solid; R_f = 0.30 (EtOAc:Hexane, 3.0:7.0); mp: 41-43 °C; ^1H NMR (600 MHz, $CDCl_3$): δ 7.31-7.29 (t, *J* = 7.2 Hz, 2H), 7.25-7.23 (t, *J* = 7.2 Hz, 1H), 7.21-7.17 (d, *J* = 7.2 Hz, 2H), 3.51-3.48 (q, 2H), 2.81-2.79 (t, *J* = 7.2 Hz, 2H), 1.92 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 139.0, 128.9, 128.6, 126.7, 40.8, 35.8, 23.4 ppm; IR (KBr): 3297, 3087, 2954, 1653, 1550, 1453, 1032, 700, 512 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{10}H_{14}NO$ 164.1070, found 164.1075.

_N_-(Pyridin-2-yl)acetamide[153] (entry 12, Table 6.1.2)



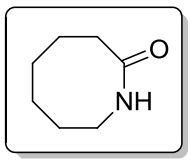
Yield: 108 mg (80%); white solid; R_f = 0.30 (EtOAc:Hexane, 3.0:7.0); mp: 146-148 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.26-8.25 (d, *J* = 7.2 Hz, 1 H), 8.22-8.21 (d, *J* = 8.4 Hz, 1 H), 7.72-7.70 (t, *J* = 7.2 Hz, 2H), 7.05-7.03 (t, *J* = 7.2 Hz, 2H), 2.20 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.1, 151.8, 147.7, 138.8, 119.3, 114.5, 24.9 ppm; IR (KBr): 3297, 2934, 1654, 1612, 1542, 763, 541 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_7H_9N_2O$ 137.0709, found 137.0714

Azepan-2-one[154] (entry 13, Table 6.1.2)



Yield: 77 mg (68%); white solid; R_f = 0.40 (EtOAc:Hexane, 2.5:7.5); mp: 67-70 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 6.50 (br, NH), 3.12-3.10 (m, 2H), 2.32-2.29 (m, 2H), 1.58-1.45 ppm (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.4, 42.1, 36.1, 30.6, 29.5, 23.1 ppm; IR (KBr): 3314, 2934, 1660, 1472, 1421, 1131, 804, 561 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_7H_{14}NO$ 114.0914, found 114.0919.

Azocan-2-one[155] (entry 14, Table 6.1.2)



Yield: 90 mg (71%); white solid; R_f = 0.40 (EtOAc:Hexane, 2.5:7.5); mp: 35-37 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 6.50 (br, NH), 3.32-3.28 (m, 2H), 2.41-2.36 (m, 2H), 1.78-1.74 (t, *J* = 7.2 Hz, 2H), 1.58-1.55 ppm (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.2, 43.4, 33.1, 30.1, 27.9, 25.5, 24.6, 23.2 ppm; IR (KBr): 3352, 2930, 1657, 1471, 1422, 1243, 1134, 895, 566 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_7H_{14}NO$ 128.1070, found 128.1075.

6.6. Selected spectra

6.6.1. ^{1}H NMR ^{13}C NMR of selected compound

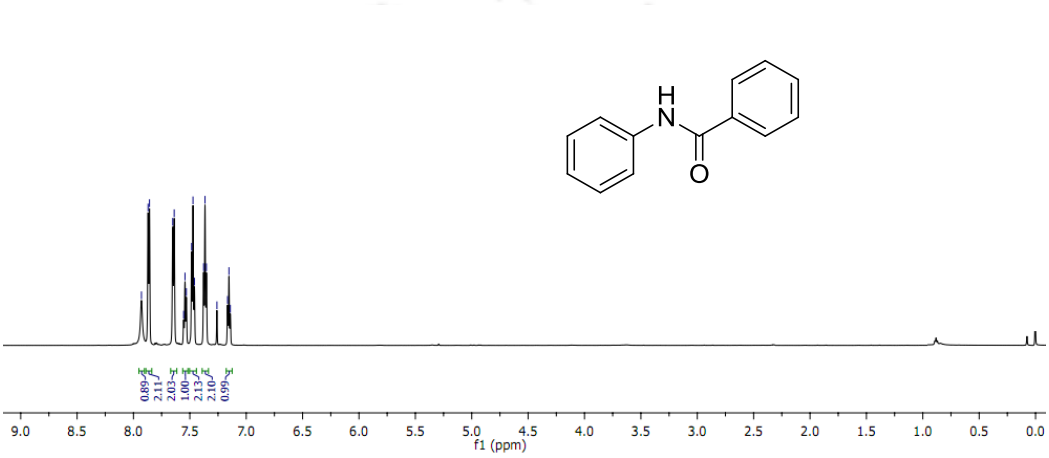


Figure S1: ^{1}H-NMR spectrum of *N*-phenylbenzamide (entry 2, Table 6.1.2)

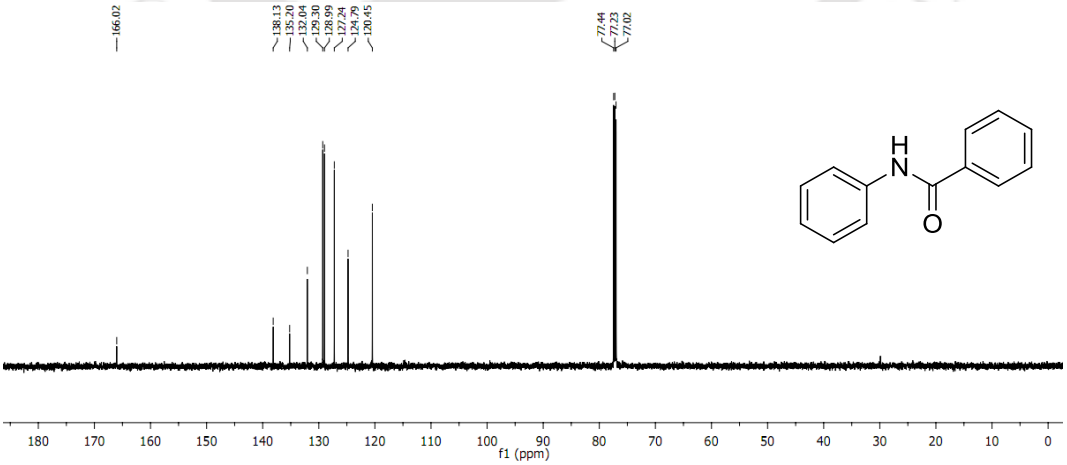


Figure S2: ^{13}C-NMR spectrum of *N*-phenylbenzamide (entry 2, Table 6.1.2)

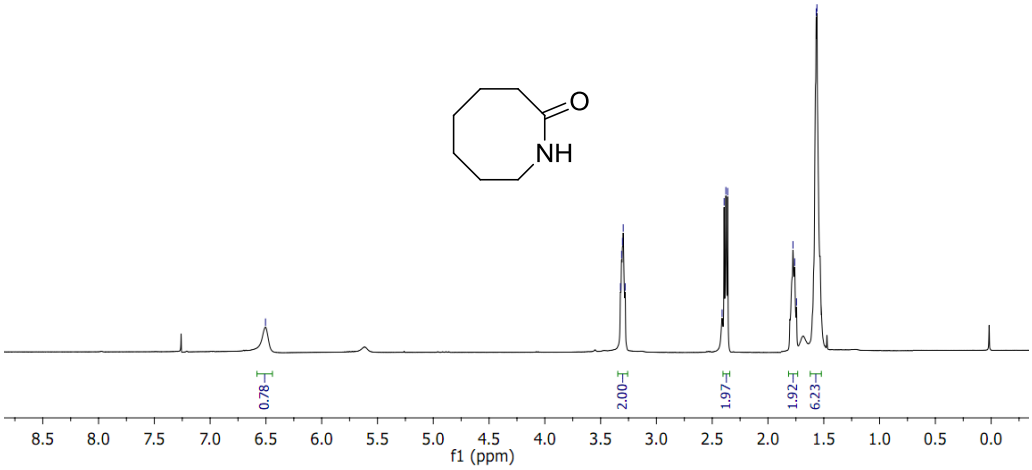


Figure S3: ^{1}H-NMR spectrum of azocan-2-one (entry 14, Table 6.1.2)

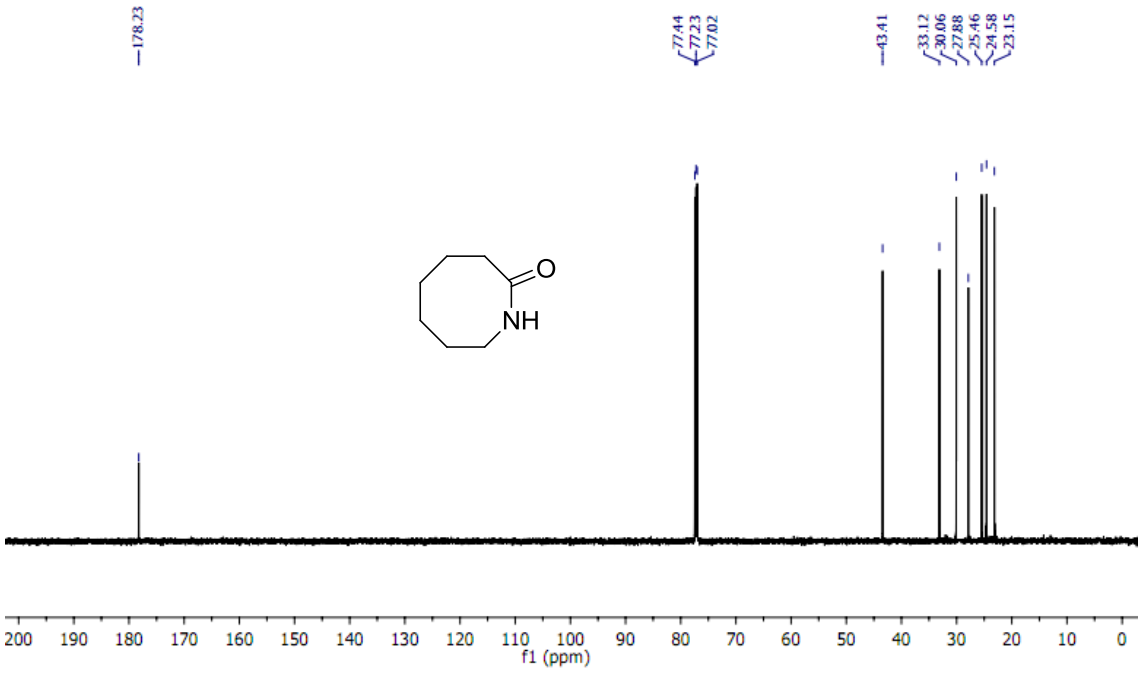


Figure S4: ^{13}C-NMR spectrum of azocan-2-one (entry 14, Table 6.1.2)

6.6.2. Mechanism study spectra

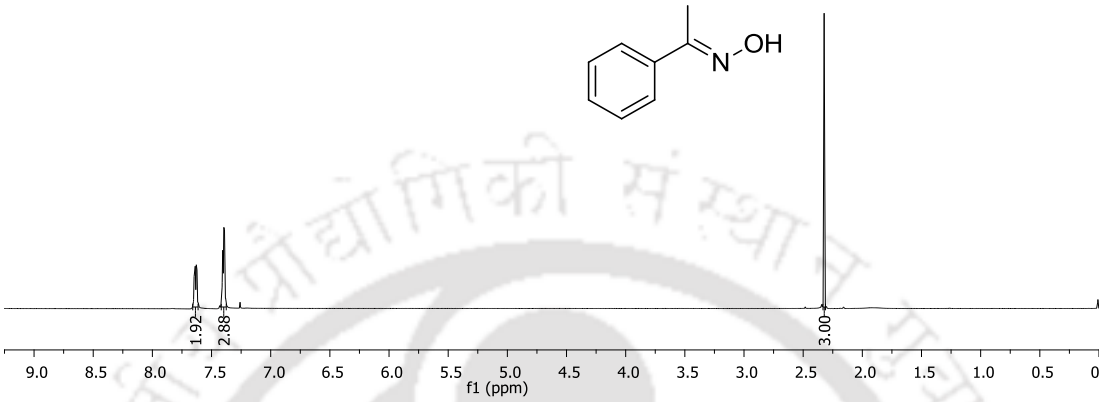


Figure S5: ^{1}H-NMR spectrum of acetophenone oxime

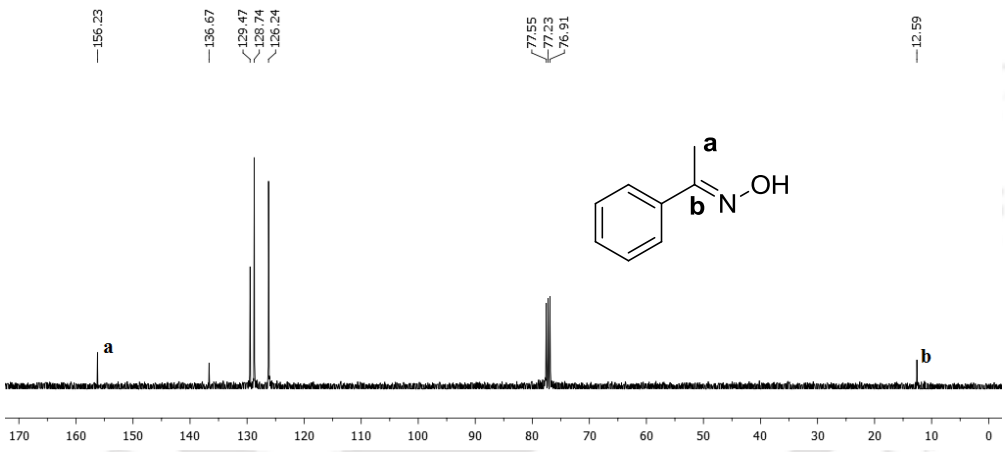


Figure S6: ^{13}C-NMR spectrum of acetophenone oxime

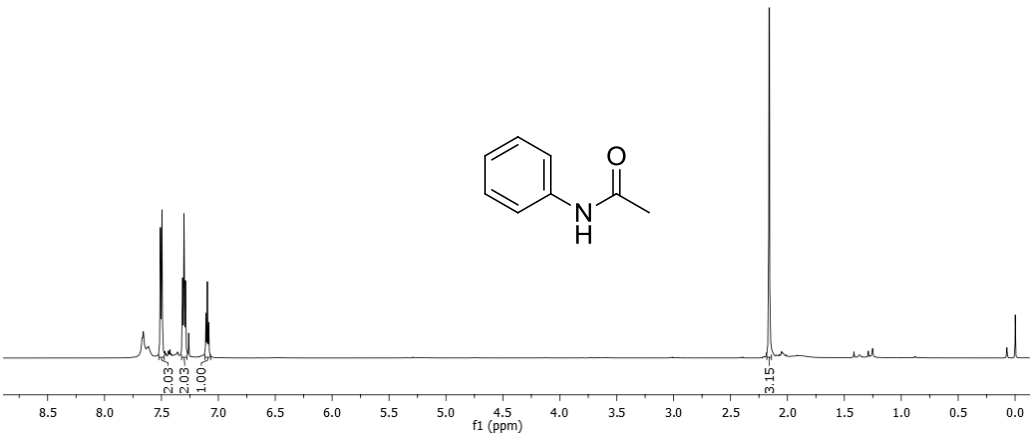


Figure S7: ^{1}H-NMR spectrum of product of acetophenone oxime (entry 1, Table 6.1.2)

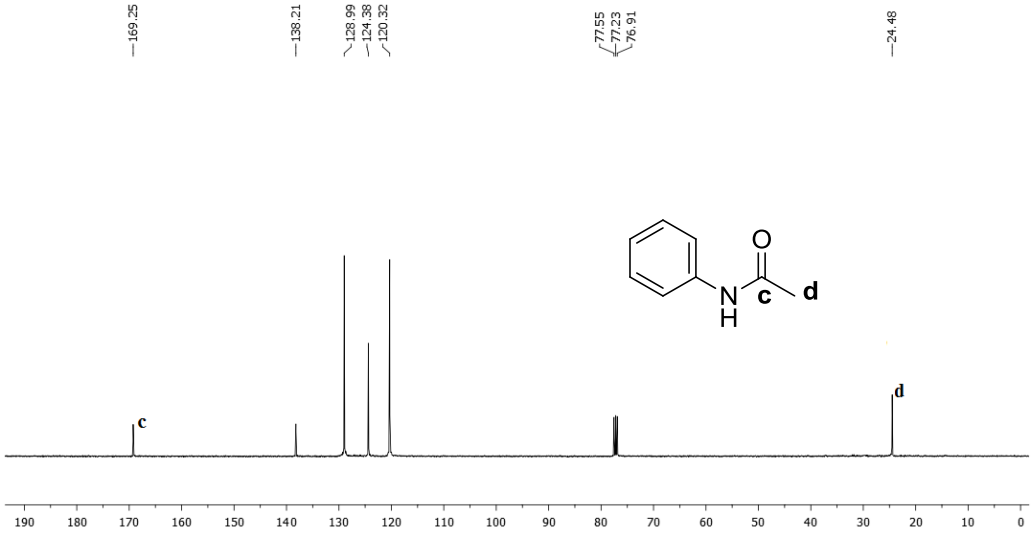


Figure S8: ^{13}C-NMR spectrum of product of acetophenone oxime (entry 1, Table 6.1.2)

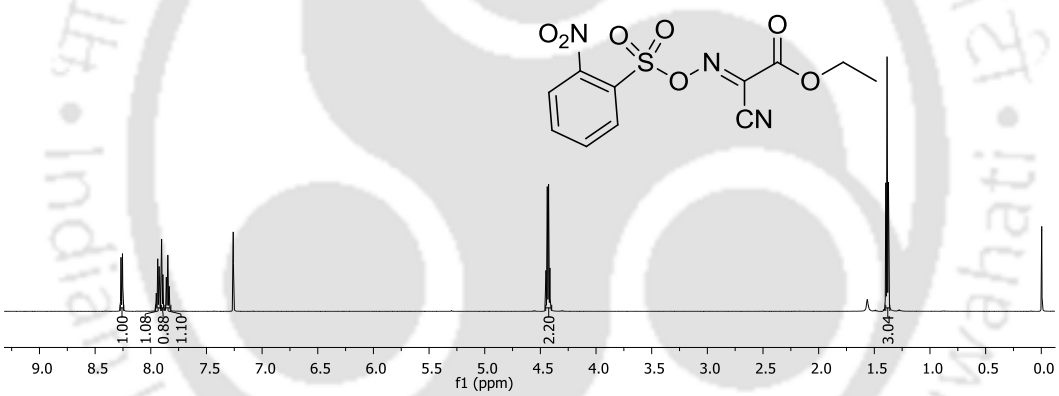


Figure S9: ^{1}H-NMR spectrum of *o*-NosylOXY

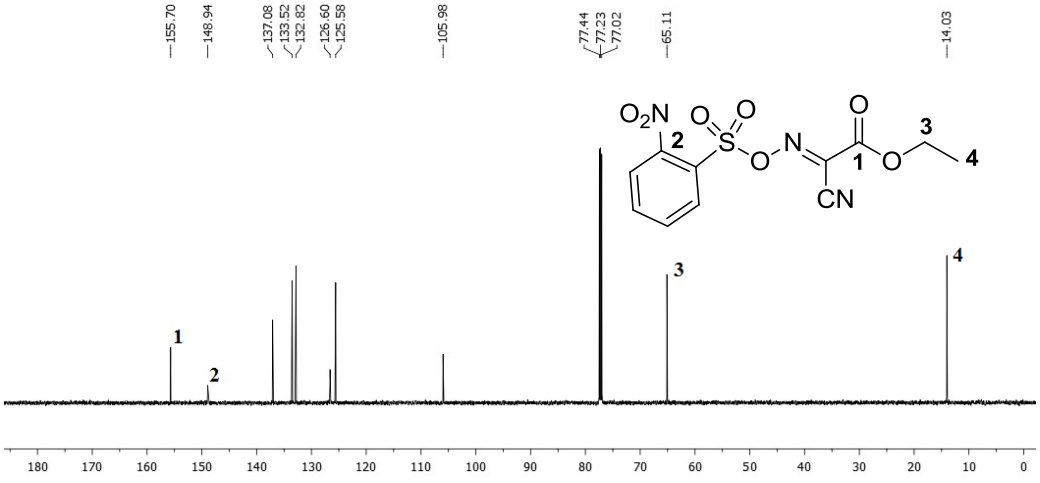


Figure S10: ^{13}C-NMR spectrum of *o*-NosylOXY

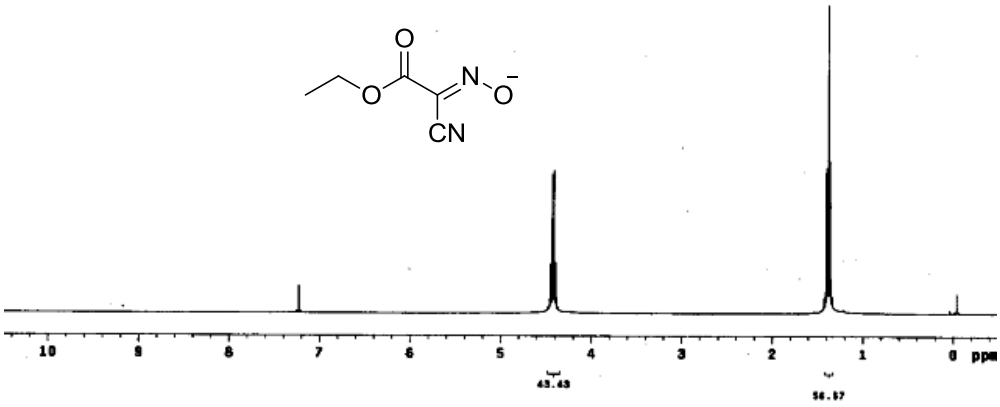


Figure S11: ^{1}H-NMR spectrum of free Oxyma

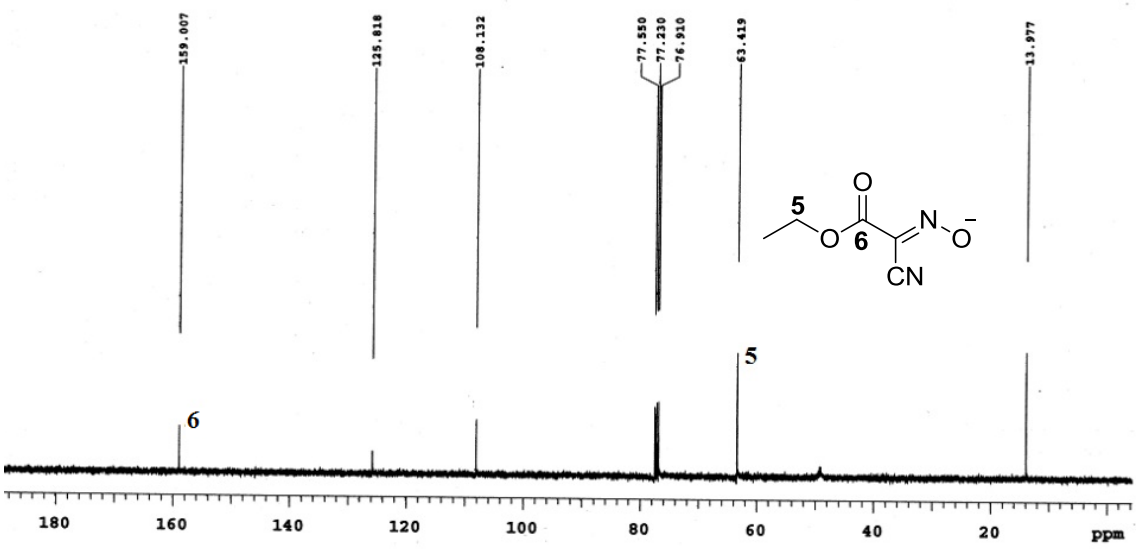


Figure S12: ^{13}C-NMR spectrum of free Oxyma

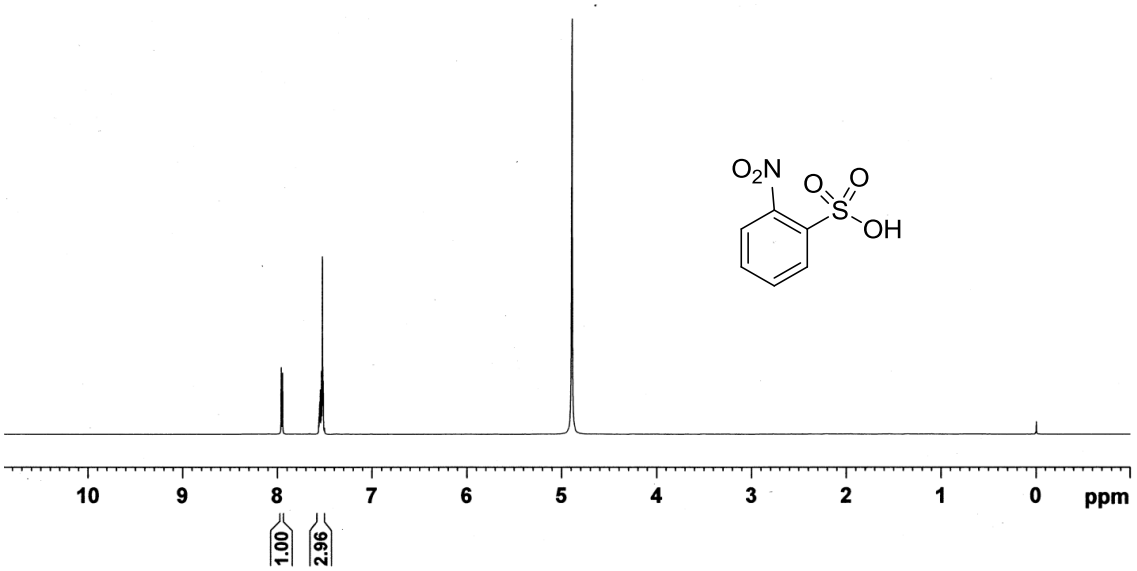


Figure S13: ^{1}H-NMR spectrum of *o*-nosylsufonic acid

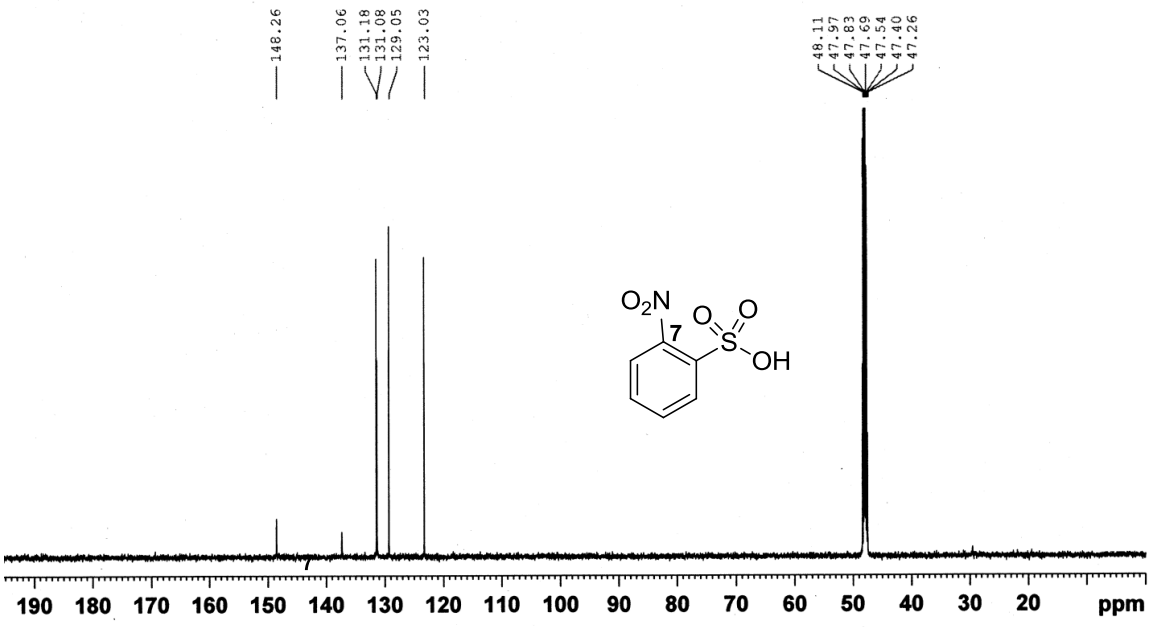


Figure S14: ^{13}C-NMR spectrum of *o*-nosylsufonic acid

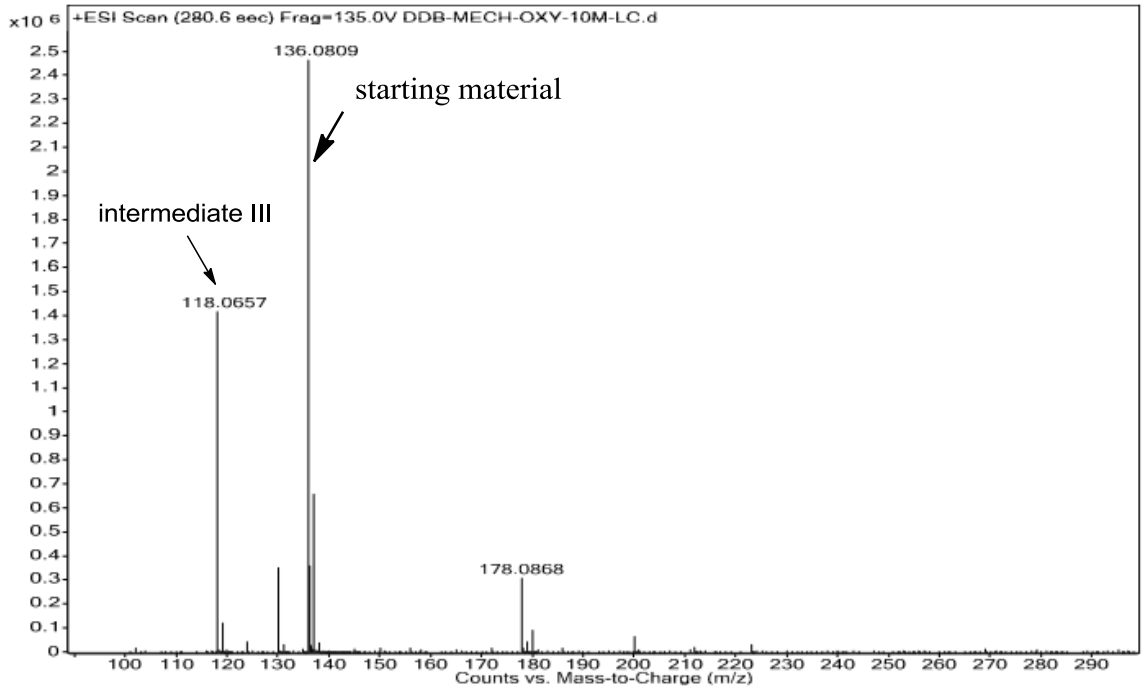


Figure S15: HRMS spectrum of Intermediate **III**

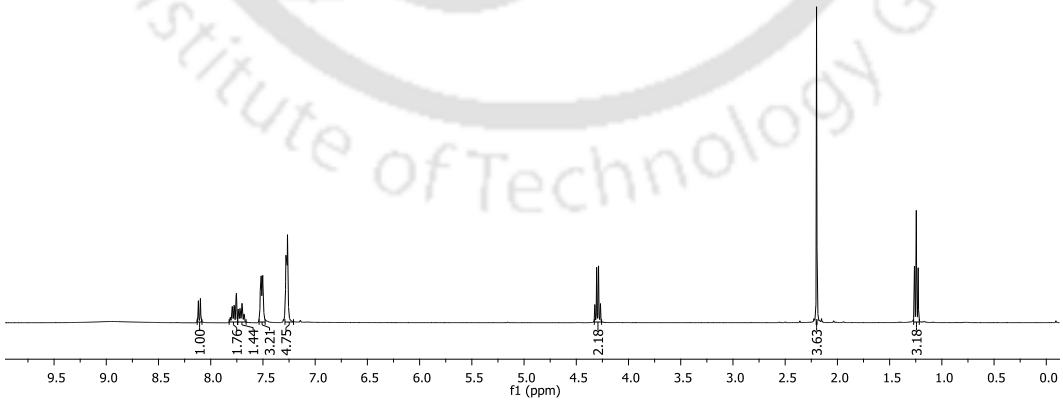


Figure S16: ^{1}H-NMR spectrum of reaction mixture at 0 minute

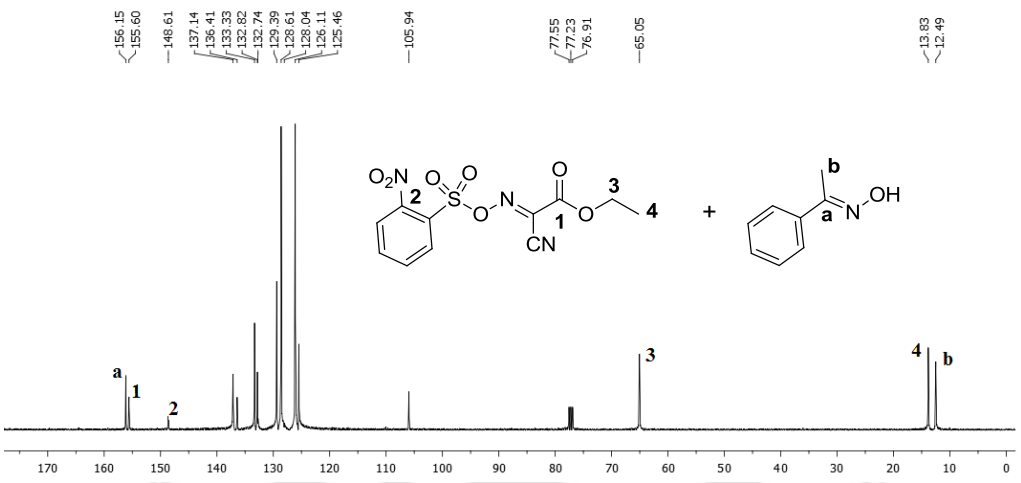


Figure S17: ^{13}C-NMR spectrum of reaction mixture at 0 minute

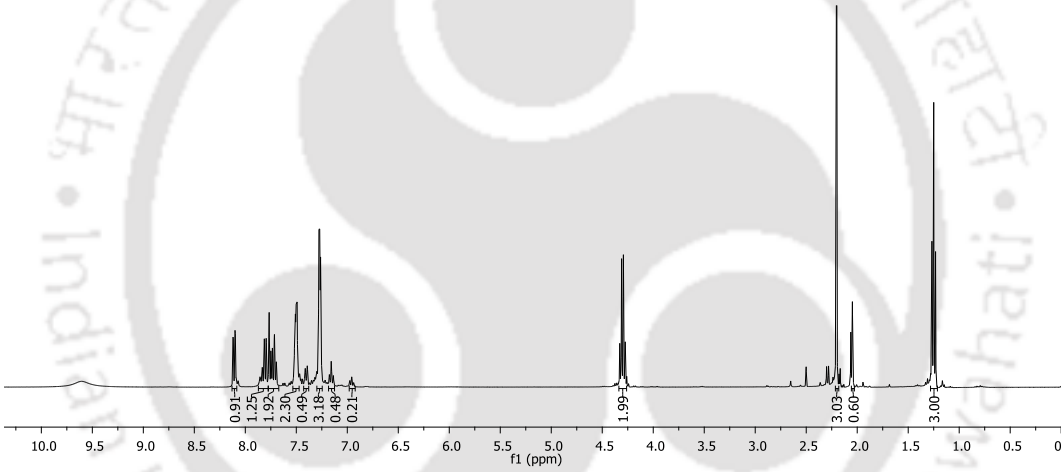


Figure S18: ^{1}H-NMR spectrum of reaction mixture at 50 minutes

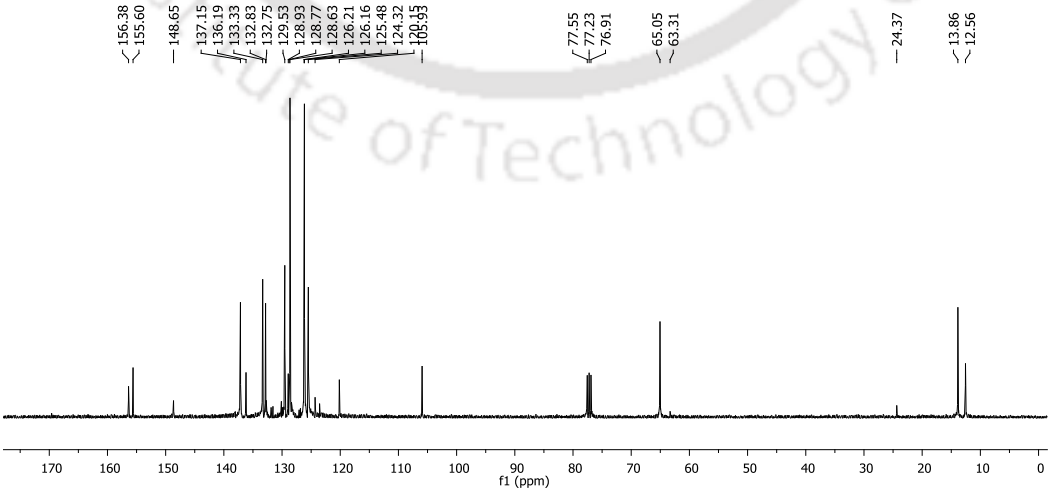


Figure S19: ^{13}C-NMR spectrum of reaction mixture at 50 minutes

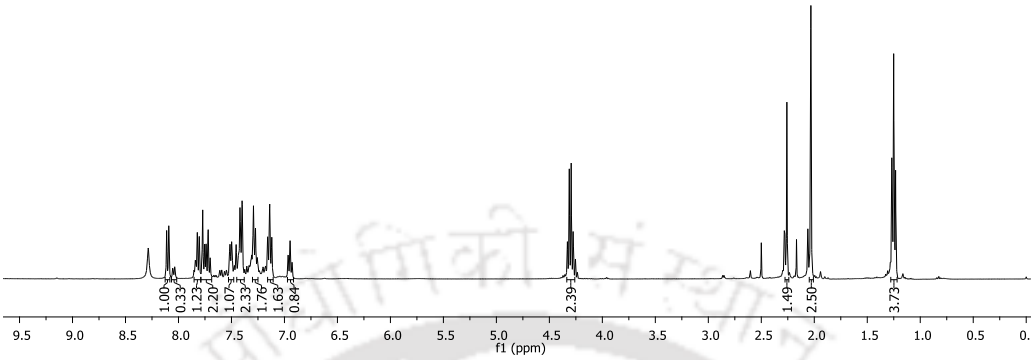


Figure S20: ^{1}H-NMR spectrum of reaction mixture at 100 minutes

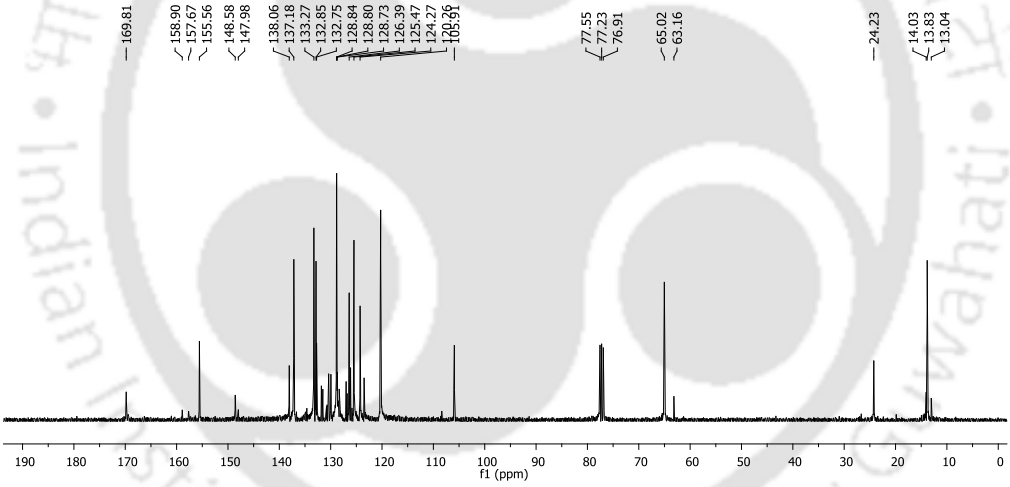


Figure S21: ^{13}C-NMR spectrum of reaction mixture at 100 minutes

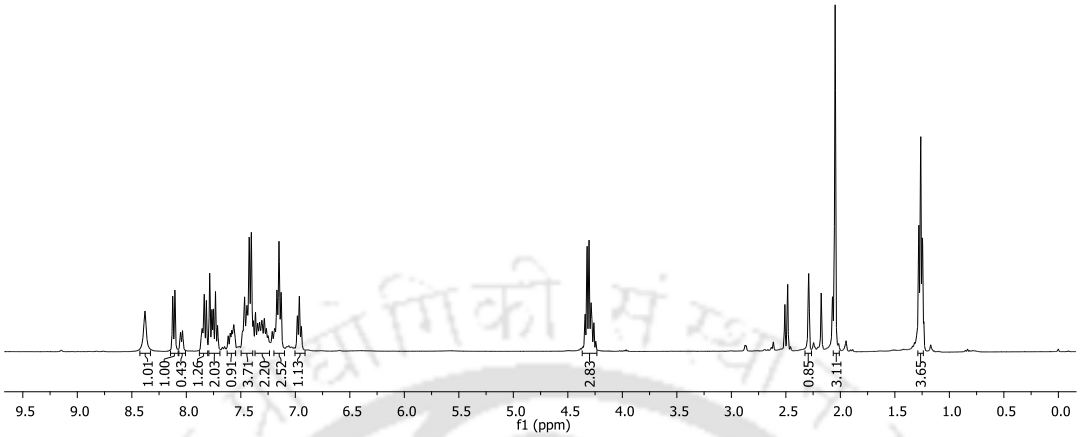


Figure S22: ^{1}H-NMR spectrum of reaction mixture at 135 minutes

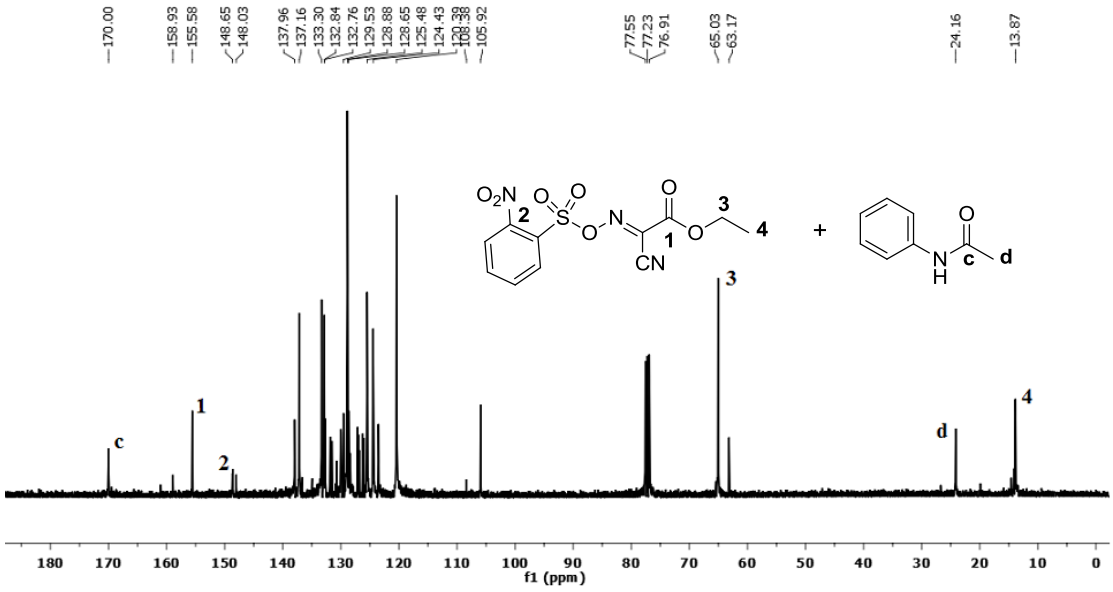


Figure S23: ^{13}C-NMR spectrum of reaction mixture at 135 minutes

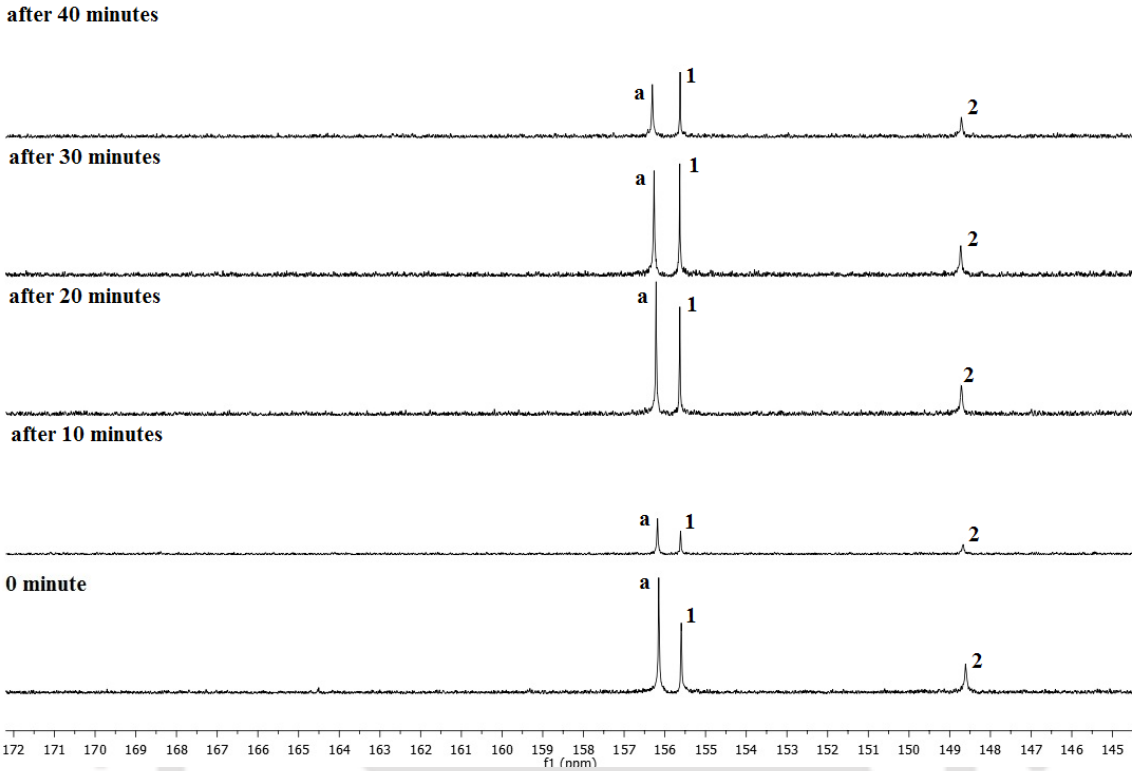


Figure S24: Time dependent ^{13}C NMR carbonyl region at 0 to 40 minutes

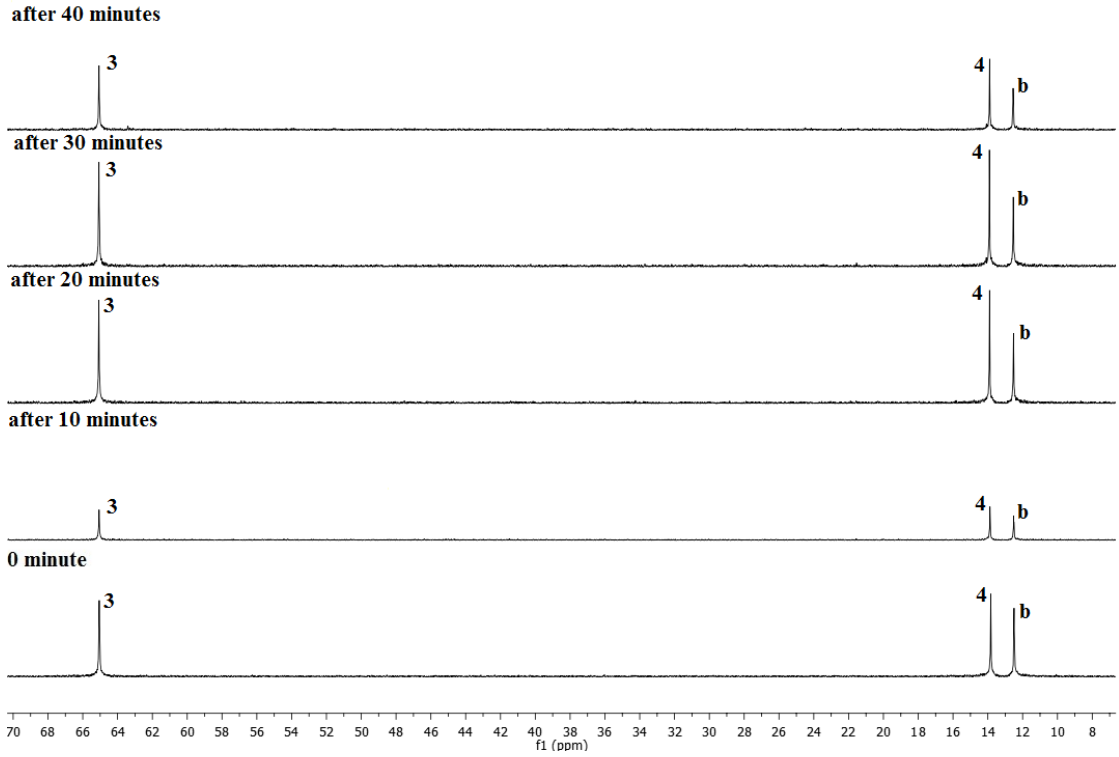


Figure S25: Time dependent ^{13}C NMR aliphatic region at 0 to 40 minutes

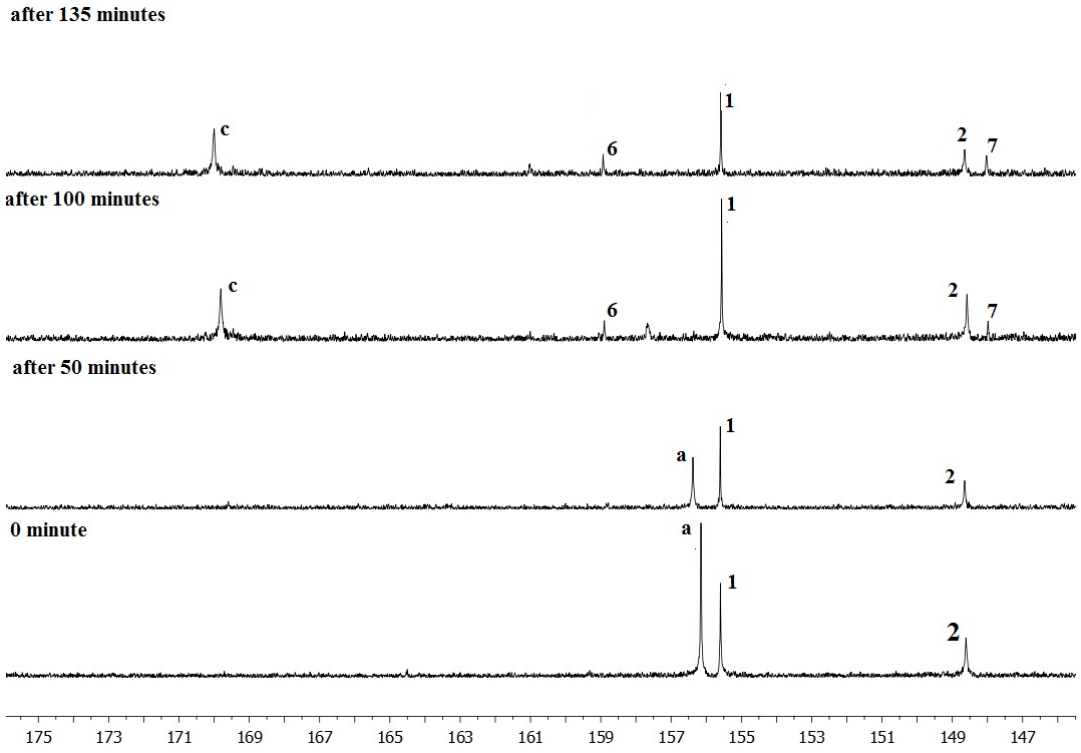


Figure S26: Time dependent ^{13}C NMR carbonyl region

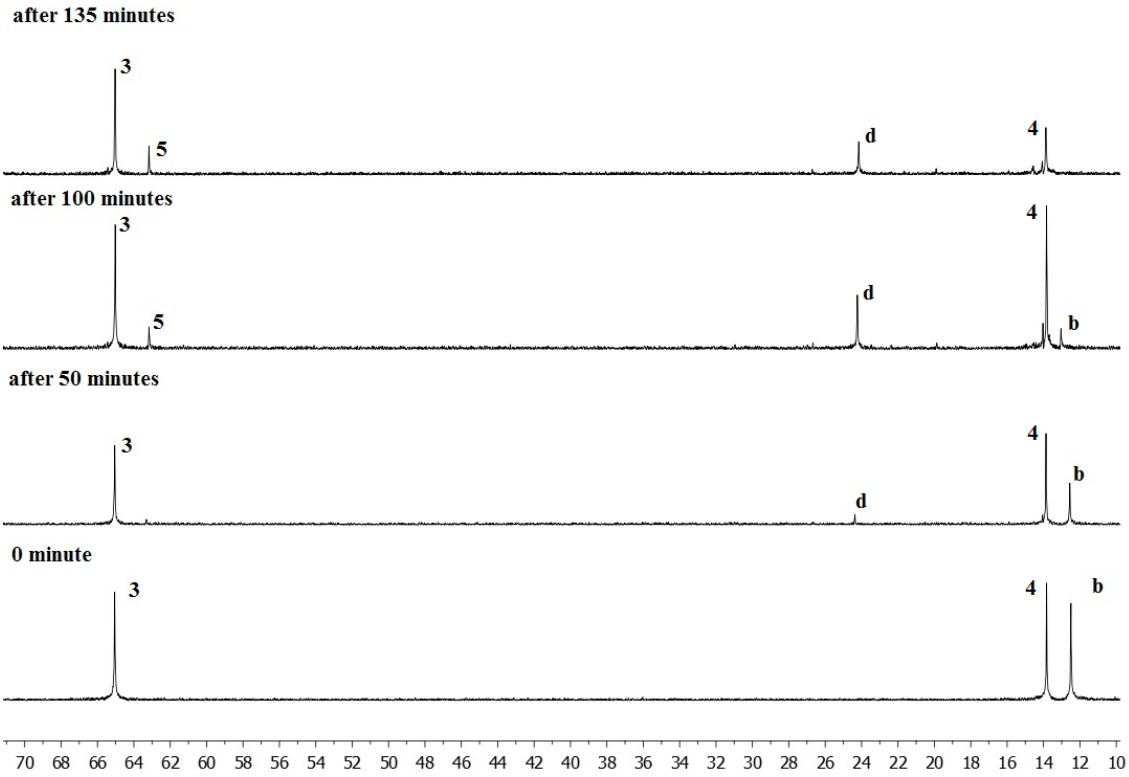
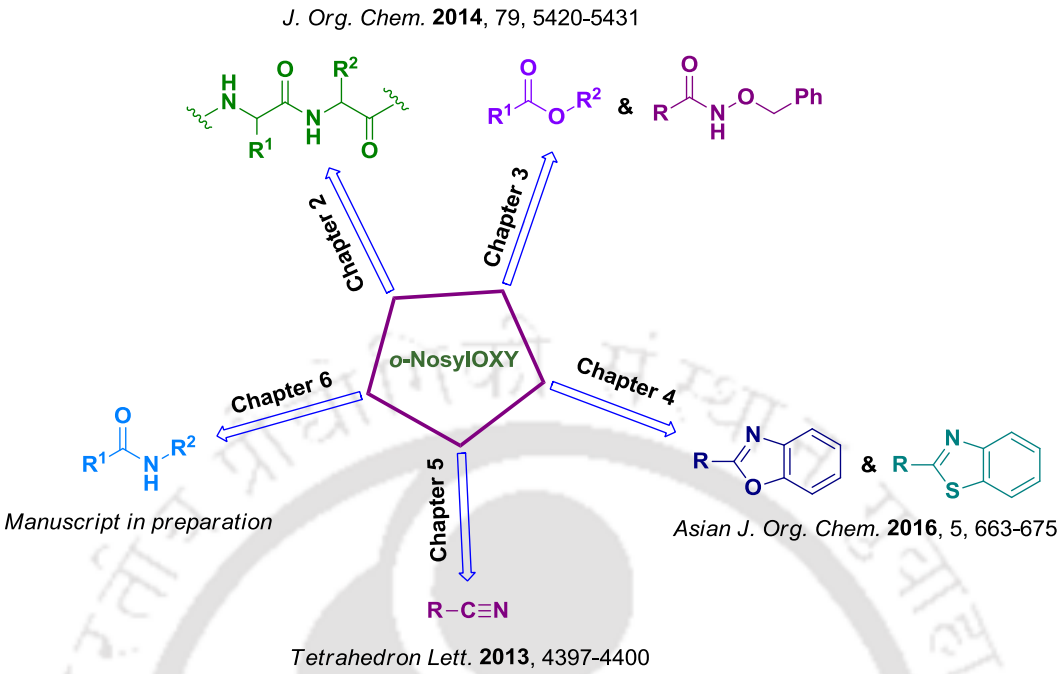


Figure S27: Time dependent ^{13}C NMR aliphatic region

Conclusions and Future Directions

Conclusions

The work presented in this thesis is focused on the development of new reagent and its application for the synthesis of amides, esters, peptides, hydroxamates, *N*-protected amino acid based benzoxazoles & benzothiazoles and nitriles. The whole structure of the thesis is depicted in scheme 1. We have developed a new coupling reagent ethyl 2-Cyano-2-(2-nitrobenzenesulfonyloxyimino)acetate (*o*-NosylOXY). In chapter 2, we have described development of *o*-NosylOXY for racemization free synthesis of amides and peptides. In chapter 3, we described the racemization free synthesis of esters and hydroxamates using *o*-NosylOXY. In chapter 4, we illustrated synthesis of benzoxazole and benzothiazole from carboxylic acid and *N*-protected amino acid by *o*-NosylOXY and *p*-TsOH. In chapter 5, we demonstrated the application of *o*-NosylOXY for nitrile synthesis. Further, in chapter 6, we described the synthesis of amide/lactam from ketoxime via Beckmann rearrangement using *o*-NosylOXY as an organocatalyst.



Scheme 1. Thesis overview

Future directions

The new coupling reagent and the methods that we developed in my Ph. D. tenure can further be used for the synthesis of cyclic peptides, oxa-peptides, aza-peptides, and many other organic transformations.

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Publications and book chapter

Publications

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Oral and poster presentation in conferences

1. **Dev, D**.; Palakurthy, N. B.; Mandal, B. Synthesis of *O*-benzyl hydroxamtes from carboxylic acids by using the *N*-hydroxy benzotriazole esters of sulfonic acids. *ChemConvene-2015*, 8th April, **2015**, Department of Chemistry, IIT Guwahati, p-10. (**Poster**)
2. **Dev, D.**; Mandal, B.; Ethyl 2-cyano-2-(2-nitrobenzene sulfonyloxyimino)acetate (*o*-NosylOXY): one of the best coupling reagent. *Research Conclave 1st edition*, 25th March, **2015**, Department of Chemistry, IIT Guwahati, OP-03. (**Oral**)
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Book chapter

Thalluri, K.; **Dev, D**.; Palakurthy, N. B.; Manne, S. R; Chandra, J.; Mandal, B. The coupling reagents the world in need indeed. *Proceeding of international conference on new dimensions in chemistry and chemical technologies applications in pharma industry*, NDCT-2014, JNTU Hyderabad, 23th-25th June, **2014**, page 348-351 (ISBN 978-93-82829-90-4).

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Qualifications

July, 2011 to Present	**Ph.D. in Chemistry** Indian Institute of Technology Guwahati, Assam, India Thesis: Development of *ortho*-NosylOXY as a Novel Coupling Reagent for Peptide Synthesis and Related Organic Transformations. Thesis Supervisor: Dr. Bhubaneswar Mandal
July 2009 to June 2011	**M.Tech in Chemistry** Indian Institute of Technology Roorkee, Roorkee, Uttarakhand, India Thesis: Synthesis and Characterization of *2*-(Substituted aryl)-*3,3a*-dihydro-*8H*-pyrazolo [*5,1-a*]isoindol-*8*-ones via Chalcone based *N*-Formyl-Pyrazolines. Thesis advisor: Dr. Naseem Ahmed
July, 2006 to June, 2008	**M.Sc. in Chemistry** Purvanchal University Jaunpur, Uttar Pradesh, India
July, 2003 to June, 2006	**B.Sc. in Chemistry with Zoology and Botany** Purvanchal University Jaunpur, Uttar Pradesh, India

Honour

Qualified Graduate Aptitude Test (GATE) with **All India Rank-701**, held on March, 2009 in Chemistry, organized by Ministry of Human Resource Development, Government of India

Research Experiences

- I have worked on development of coupling reagent and its application for the peptide synthesis, ester, hydroxamate, benzoxazole, benzothiazole and nitrile synthesis during my Ph.D. research.
- During my Ph.D. term, I mainly focused on the development of new coupling reagent. I have developed Oxyma based coupling reagent, Ethyl 2-Cyano-2-(2-nitrobenzenesulfonyloxyimino)acetate (*o*-NosylOXY). It is used for the racemization free synthesis of amide, ester, hydroxamate and peptide.
- During my Ph.D. tenure, I have prepared oligopeptide $hIAPP_{22-27}$ (human islet amyloid polypeptide) fragment NFGAILG and ACP_{65-74} (acyl carrier protein (65−74) fragment) using Fmoc/^{t}Bu orthogonal protection technique based SPPS by reagent *o*-NosylOXY.
- During my Ph.D tenure, I have also synthesized heterocyclic compound benzoxazole and benzothiazole from carboxylic acid and *N*-protected amino acid in solution using *o*-NosylOXY.

Academic and Professional Skills

- **Laboratory and Instrumentation:** Familiar with Synthetic Organic Chemistry, peptide synthesis (solution phase and solid phase), NMR Spectroscopy (1D, 2D), HPLC, Mass Spectrometry (ESI, MALDI), GCMS, FT-IR spectroscopy, Polarimeter.
- **Software:** Origin, Chem Draw, Adobe Illustrator, MS-Office, Adobe Photoshop, Spin works and MestRenova.
- **Teaching Experience:** Worked as Teaching Assistant (TA) in B.Tech and M.Sc Laboratory at IIT Guwahati, India.
- **Language:** Hindi, English and Bhojpuri.

Research Interests

- Protein and Peptide Chemistry.
- Synthetic Organic Chemistry.
- Heterocyclic Synthesis.