Metal- and Organo-Catalyzed Stereoselective Transformation of *γ/δ*-Hydroxyenones

A Dissertation

Submitted in partial fulfilment of the

Requirements for the Degree of

Doctor of Philosophy

by

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Dedicated

to

My Parents and Brother

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

STATEMENT

I, hereby declared that the work comprised in this thesis entitled "***Metal- and Organo-Catalyzed Stereoselective Transformation of γ/δ-Hydroxyenones***" is the outcome of the research work carried out by me under the supervision of Dr. Subhas Chandra Pan, Department of Chemistry, Indian Institute of Technology Guwahati, India, for the award of the degree of Doctor of Philosophy.

In harmony with the general practice of reporting scientific observations, due acknowledgements have been made if the work is established on the findings of other investigators.

Guwahati

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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled "***Metal- and Organo-Catalyzed Stereoselective Transformation of γ/δ-Hydroxyenones***" which is being submitted to the Indian Institute of Technology Guwahati for the award of Doctor of Philosophy in Chemistry by Mr. Keshab Mondal (Roll No: 126122006) was carried out by him under my supervision at this institute. The work presented in his thesis is original and that has not been submitted elsewhere for a degree.

Guwahati — Dr. Subhas Chandra Pan

February, 2018 — Supervisor

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Sincerely,
Keshab Mondal

CONTENTS

Abbreviation

Ac	Acetyl
APCI	Atmospheric pressure chemical ionization
Å	Angstrom
Ar	Argon
br.	Broad
Bn	Benzyl
Bu	Butyl
CCDC	Cambridge crystallographic data centre
COSY	Correlation spectroscopy
COD	1,5-Cyclooctadiene
CSA	Camphorsulfonic acid
CPME	Cyclopentyl methyl ether
Cy	Cyclohexyl
^{o}C	Degree celsius
d	Doublet or day
δ	Chemical shift or delta
DA	Donor-acceptor
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]- undec-7-ene
DCE	Dichloroethane
DCM	Dichloromethane
DEPT	Distortionless enhancement by polarization transfer
DIPEA	*N*,*N*-Diisopropylethylamine
DME	Dimethoxyethane
DMF	N,N-Dimethylformamide
DMAP	4-(Dimethylamino)pyridine
DMSO	Dimethylsulfoxide
dr	Diastereomeric ratio
EtOAc	Ethyl acetate
ee	Enantiomeric excess
equiv.	Equivalent
ESI	Electrospray ionization
Et	Ethyl
EWG	Electron withdrawing group
EDG	Electron donating group
g	Grams
γ	Gamma
h	Hours
HFIP	Hexafluoroisopropanol
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
Hz	Hertz

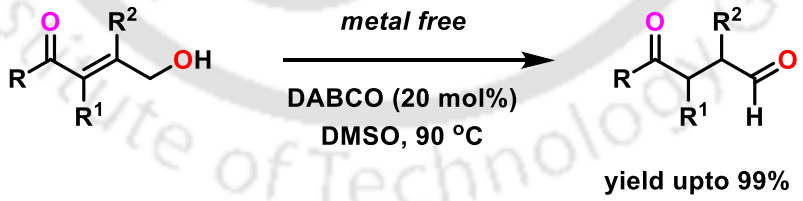
i	Iso
FT-IR	Fourier transform infrared spectroscopy
J	Coupling constant
K_x	Rate constant
LA	Lewis acid
m	Multiplet
m	*Meta*
mCPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl
mg	Miligram
mL	Mililitre
mmol	Milimole
Mp	Melting point
MS	Molecular seive
MTBE	Methy tertiary butyl ether
NMR	Nuclear magnetic resonance
NOESY	Nuclear overhauser enhancement spectroscopy
o	*Ortho*
ω	Omega
ORTEP	Oak ridge thermal ellipsoid plot program
p	*Para*
Ph	Phenyl
Pr	propyl
ppm	Parts per million
PTA	1,3,5-triaza-7-phosphaadamantane
p-TSA	*p*-Toluenesulfonic acid
q	Quartet
rt	Room temperature
s	Singlet
TBD	1,5,7-Triazabicyclo[4.4.0]-dec-5-ene
THF	Tetrahydrofuran
t	*Tert*
TMS	Tetramethylsilane
TMG	1,1,3,3-tetramethylguanidine
Tol	Tolyl
Ts	Tosyl
Tr	Trityl
TfOH	Triflic acid
uv	Ultra violet
XRD	X-ray diffraction

Abstract

The contents of the present thesis entitled as "***Metal- and Organo-Catalyzed Stereoselective Transformation of γ/δ-Hydroxyenones***" have been divided into five chapters based on the results achieved from the experimental works performed during the entire course of the PhD research programme.

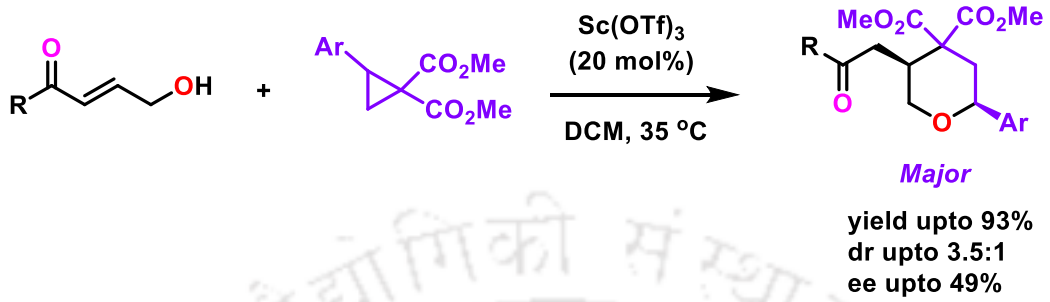
Chapter 1 contains a brief introduction and the literature review of *γ*/*δ*-hydroxyenones including different strategies for the synthesis of useful products from hydroxyenone derivatives and also have been utilized in several asymmetric as well as non-asymmetric transformation reactions.

Chapter 2 demonstrates an efficient and atom-economic method for the facile synthesis of 1,4-ketoaldehydes from organocatalytic redox isomerization of electron-deficient allylic alcohols. 20 mol% of DABCO catalyst in DMSO solvent at 90 °C has been found the best conditions for the isomerization of *γ*-hydroxyenones. This protocol is quite general to access the isomerized products in a wide range of substrates with good to excellent yields. In addition, mechanistic studies (kinetic and deuterium labelling experiments) were performed to understand the plausible reaction pathway involved for the isomerized product formation which are discussed in this section in details. Different *α*- and *β*-substituted enones were also well participated under the reaction conditions furnishing the products with moderate yields.

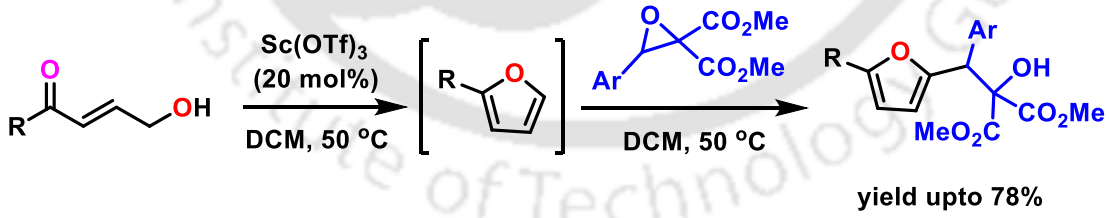


Chapter 3 describes a general route to access highly substituted tetrahydropyrans *via* $Sc(OTf)_3$ catalyzed [3 + 3] annulation of donor-acceptor cyclopropanes with *γ*-hydroxyenones in DCM solvent at 35 °C providing the desired products with *cis*-diastereoselectivities. The relative stereochemistry of the final product was determined by 2D NMR studies. The generality of the reaction permitted the synthesis of tetra-substituted tetrahydropyrans bearing aryl, alkyl, and heteroaromatic groups. A catalytic

asymmetric variant of this process is also studied preliminary using chiral PyBOX ligand. The synthetic utility of this method was also illustrated by performing different reactions using tetrahydropyran derivatives.

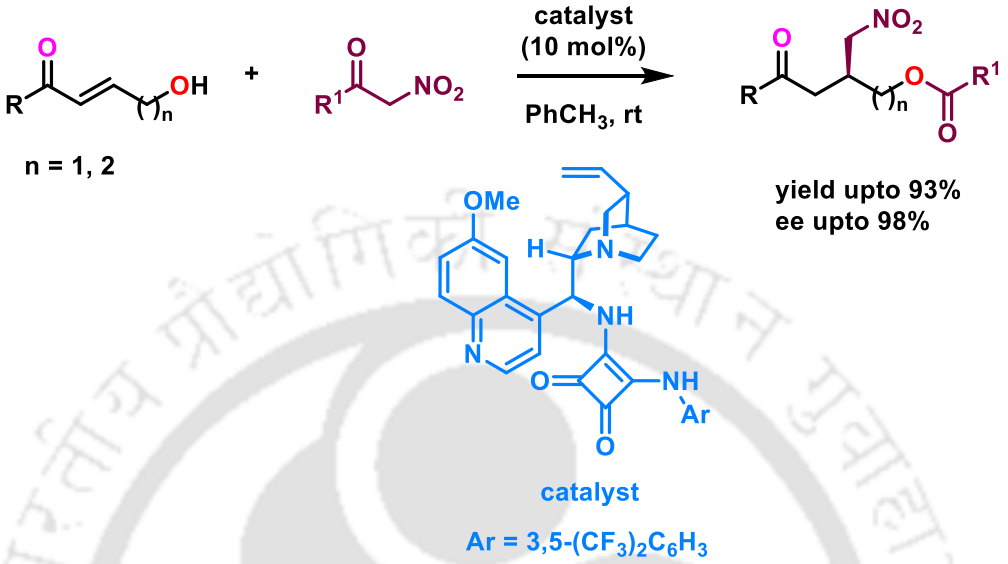


Chapter 4 illustrates the development of a new and convenient method for the synthesis of 2,5-disubstituted furans by employing the reaction between donor-acceptor oxiranes with γ-hydroxyenones under the catalysis of $Sc(OTf)_3$ (20 mol%) in DCM solvent at 50 ^{o}C with moderate to good yields which were achieved through one pot two-step reaction. The scope of the reaction is quite decent, allowing for the synthesis of disubstituted furans having aryl and heteroaromatic groups. The Hammett study was revealed to understand the electronic substituent effect on the reaction and it was observed that electron donating groups were provided better yields compared to the electron withdrawing groups present in the aryl oxirane ring. The short reaction time and mild reaction conditions are some of the salient features of this protocol. A few synthetic transformations of this method were also demonstrated in this chapter.



Chapter 5 highlights an organocatalytic asymmetric domino Michael/acyl transfer reaction between γ/δ-hydroxyenones and α-nitroketones. The quinine-derived bifunctional amino-squaramide catalyst was found to be the best catalyst in toluene solvent at ambient temperature for this reaction. The products having nitro, keto and ester functionalities were obtained with high yields and excellent enantioselectivities. The scope of this reaction is quite broad for different substrates such as alkyl, aryl as

well as heterocyclic moieties. The applicability of this method was also explored in this chapter by the synthesis of pyrrolidine motif which is present in a wide range of biologically active compounds.



Each of these chapters contain introduction, previous reported works, present result and discussion, experimental section, references, along with characterization data of products including few selective spectral data. Overall, this thesis demonstrates some new and efficient approaches for the synthesis of different functionalized target compounds based on the asymmetric and non-asymmetric transformation reactions using γ/δ-hydroxyenones.

Chapter 1

Introduction to γ/δ-Hydroxyenones

1.1 Introduction

One of the primary focus of a synthetic organic chemist is to generate complex architectures with high atom economy from inexpensive and easily available starting materials. Nowadays, scientists use to pay great attention to the chemical reactions associated with highly selective, efficient and eco-friendly manner for the application in academic as well as for industrial purpose. The formation of carbon skeletons through carbon-carbon bond formation and functionalization of suitable carbon atom to different functional groups is a significant tool in organic synthesis. Thus, different approaches have been reported for the formation of C−C bonds by reaction of a variety of carbon-nucleophiles with various carbonyl or conjugated carbonyl systems namely the aldol and Claisen condensation reaction, Grignard reaction and Michael reaction. Amongst, the Knoevenagal reaction is one of the finest tools for the elongation of convenient carbon chain to obtain *α,β*-unsaturated systems.[1]

The synthesis of heterocyclic moiety has gained great impact due to its presence in a variety of natural products and biologically active compounds.[2] In this light, the chemistry of *γ/δ*-hydroxyenones has emerged to serve a significant role in organic chemistry owing to their unique reactivity profile and demonstrated a variety of transformation reactions. The stereoselective synthesis of *γ*-hydroxyenones[3] is an important area as it is present in a variety of natural products shown in Figure 1.[4]

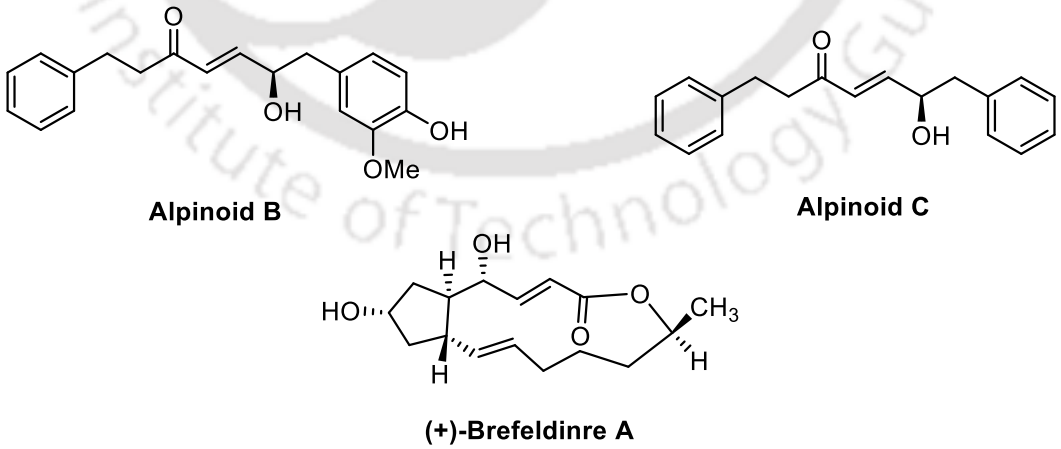


Figure 1: Examples of *γ*-hydroxyenone motif containing natural products

Over the last decades, the synthesis of *γ*/*δ*-hydroxyenones were extensively developed as it is useful for the construction of various *O*-heterocycles. Indeed, several methods for the synthesis of hydroxyenones[5] and its applications have been reported in the last decades. Recently, a number of chemists have given considerable efforts to attain these compounds in an easier process with simple starting materials[5]. Hydroxyenones are the versatile intermediates or building blocks[6] in asymmetric synthesis for the preparation of various synthetically useful bioactive compounds such as tetrahydrofuran,[7] 1,3-oxazolidine,[8] and 2-oxazolidinone[9] etc.

1.2 Reactive sites of hydroxyenones

The reactivity profile of hydroxyenones can be attributed to the different reactive sites present in this moiety (Figure 2). The hydroxyl group of it shows its oxy-nucleophilic nature. Hydrogens attached near the hydroxyl carbon are acidic in nature which are easily susceptible to be abstracted by base and the *α*,*β*-unsaturated enone motif behaves as Michael-acceptor. Due to the presence of these reactive sites, hydroxyenones are used as bidentate ligands or 1,3-conjunctive reagents (nucleophile as well as electrophile) and react with different types of dipolar reagents. Hence, hydroxyenones have widely been exploited as synthons for the synthesis of variety of useful structures in organic synthesis.

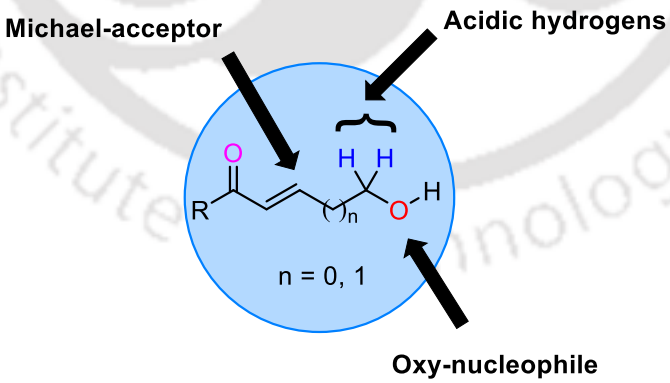


Figure 2: Reactive sites of hydroxyenones

1.3 Reported reactions with hydroxyenones

The formation of C−C and C−X (X = O, N) bonds is a powerful tool in organic chemistry. Thus, hydroxyenones were employed as precursor in different types of asymmetric reactions such as Michael reactions, cycloaddition reactions, cyclization reactions and cyclopropane ring formation reactions (Figure 3) as well as non-asymmetric reactions to attain the target compounds which can be transferred to a variety of essential compounds in organic chemistry.

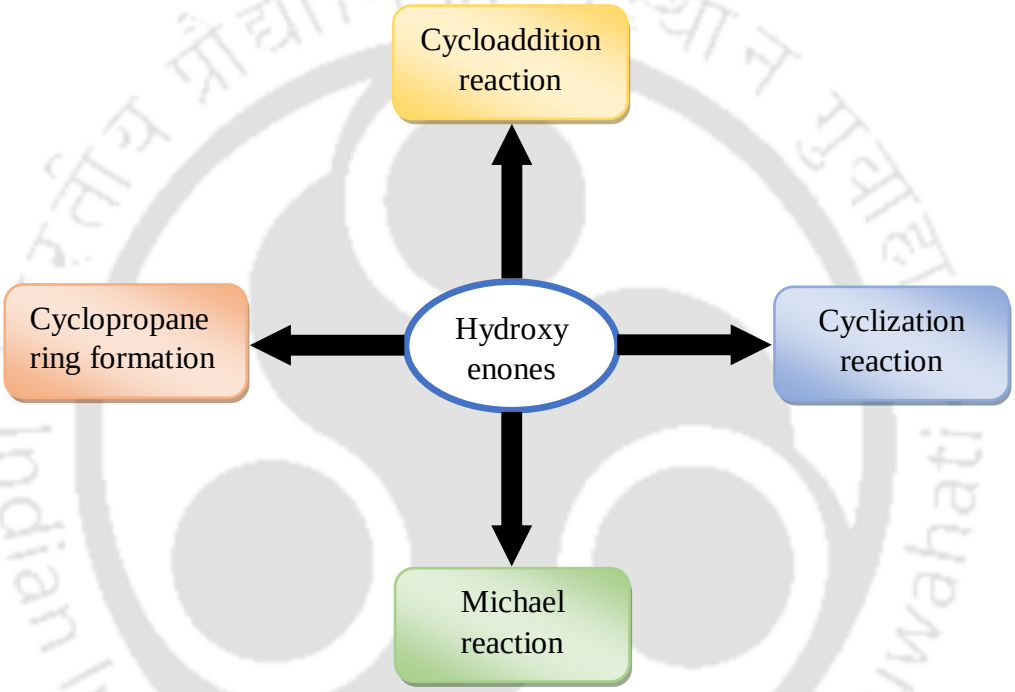


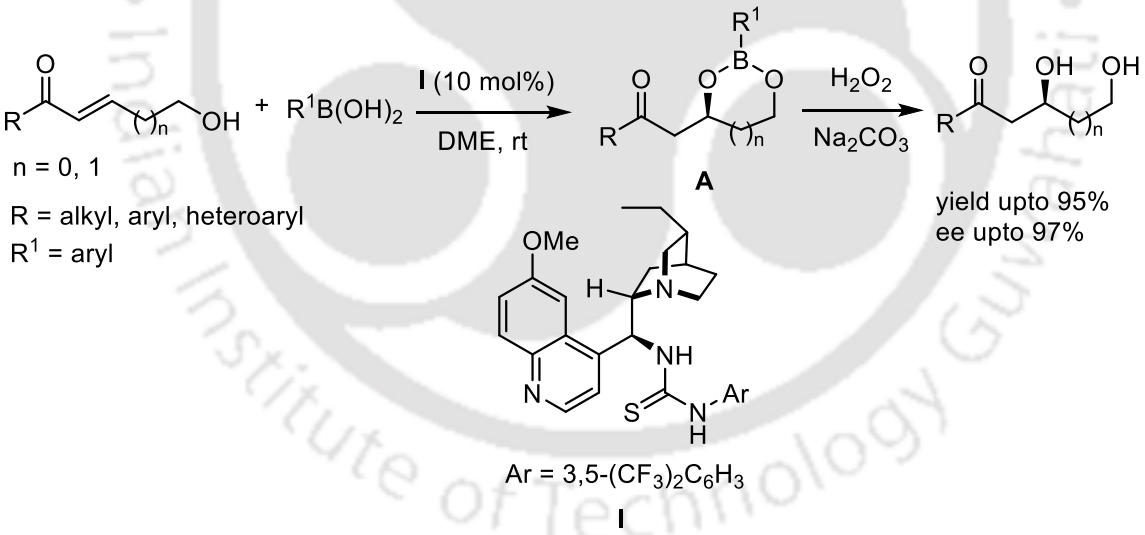
Figure 3: Different types of reaction with hydroxyenones

A. Cycloaddition reaction

Cycloadditions[10] are one of the fundamental reaction processes which have been utilized with great success for the construction of a variety of heterocyclic skeletons. In particular, 1,3-dipolar cycloadditions are common method for the preparation of five, six and seven-membered heterocyclic compounds *via* [3 + 2],[11] [3 + 3][12] and [4 + 3][13] cycloaddition reactions with different dipolarophiles. These heterocycle moieties have wide applications in pharmaceuticals and agrochemicals. Therefore, the development of heterocycle synthesis is a valuable task for the ultimate preparation of natural products

and bioactive drug molecules. Several methods have been reported for the synthesis of complex molecules utilizing hydroxyenones and few examples are listed below.

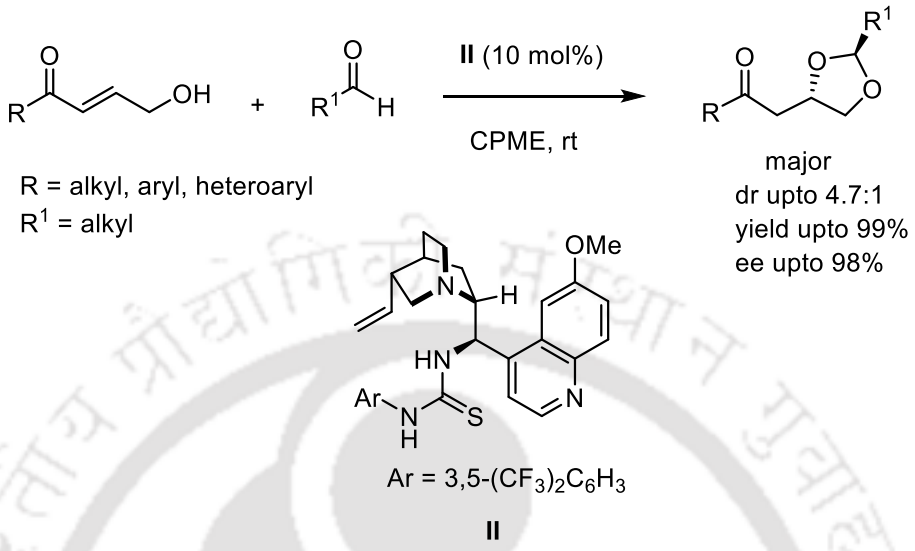
At the end of 2001, Watanabe and co-workers[14a] developed asymmetric oxy-Michael reaction between chiral ketone (derived from D-glucose and D-fructose) and *γ*/*δ*-hydroxyenones in the presence of catalytic amount of base. Later, Taylor *et al.* demonstrated hydroxide base catalyzed oxy-Michael reaction followed by intramolecular Michael dimerization reaction of *γ*-hydroxyenones for the synthesis of tetrahydrofuran derivatives.[14b] After few years, in 2008, Falck *et al.*[15] reported organocatalytic asymmetric oxy-Michael addition reaction of *γ*/*δ*-hydroxyenones with boronic acid for the formation of dioxaborolane (n = 0) or dioxaborinane (n = 1) **A** *via* hemiacetal intermediate under the catalysis of hydroquinine-based thiourea catalyst **I** (Scheme 1.1). After the treatment of compound **A** with hydrogen-peroxide, it led to the construction of chiral *β*-hydroxy carbonyl compounds. These structural motifs have served as an important synthetic intermediates and present in a variety of natural products.[16]



Scheme 1.1: Hydroquinine based oxy-Michael reaction

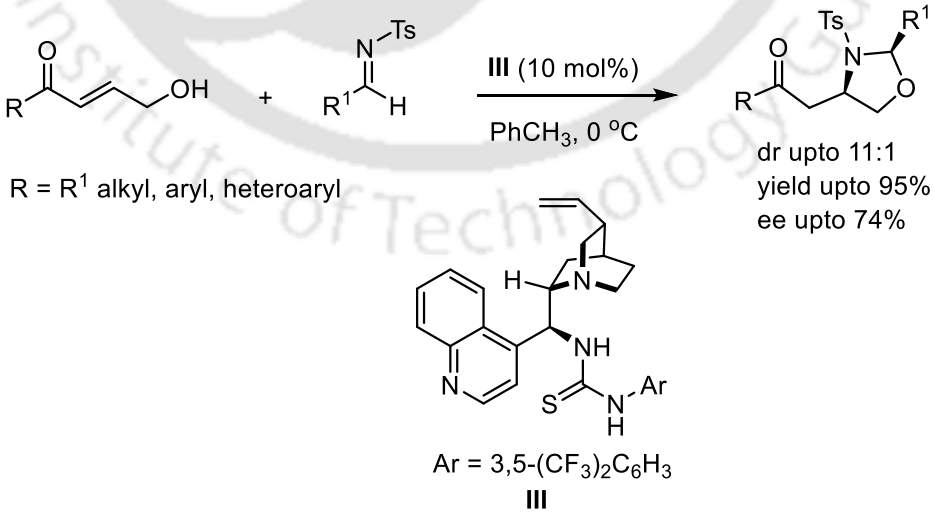
Consequently, Matsubara group[17] demonstrated a novel [3 + 2] cycloaddition reaction for the synthesis of chiral 1,3-dioxolane (cyclic acetal) from *γ*-hydroxyenones and aldehydes *via* hemiacetal intermediate in the presence of cinchona-alkaloid derived bifunctional thiourea catalyst **II** (Scheme 1.2). This group obtained the desired product

with excellent yields and high enantioselectivities but the diastereomeric ratio was not satisfactory.



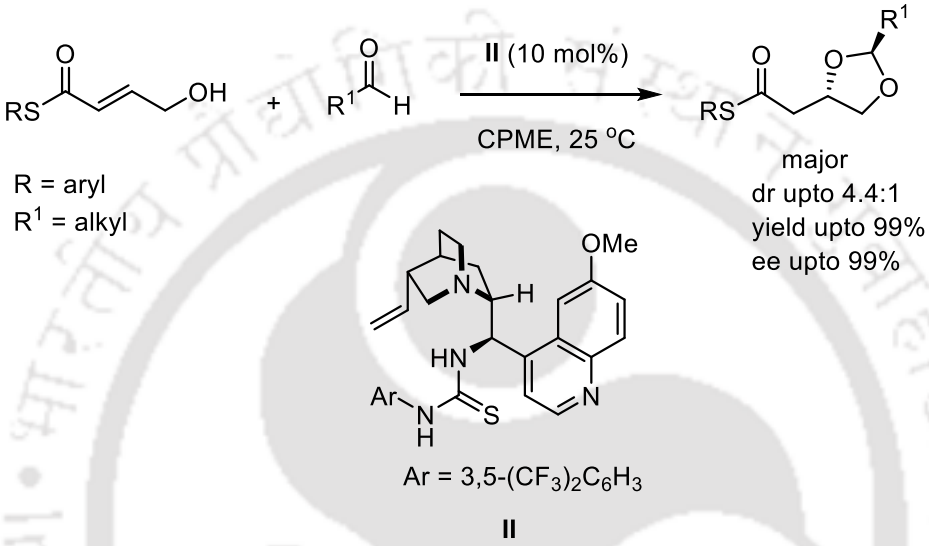
Scheme 1.2: Asymmetric synthesis of 1,3-dioxolanes

Further, to improve the diastereoselectivity, the same group performed the reaction with tosyl-imine instead of aldehyde for the construction of asymmetric 1,3-oxazolidine using cinchonidine-derived bifunctional catalyst **III** and moderate enantioselectivity was obtained (Scheme 1.3).[18] These skeletons are useful in pharmaceutical chemistry as well as building block in organic synthesis.



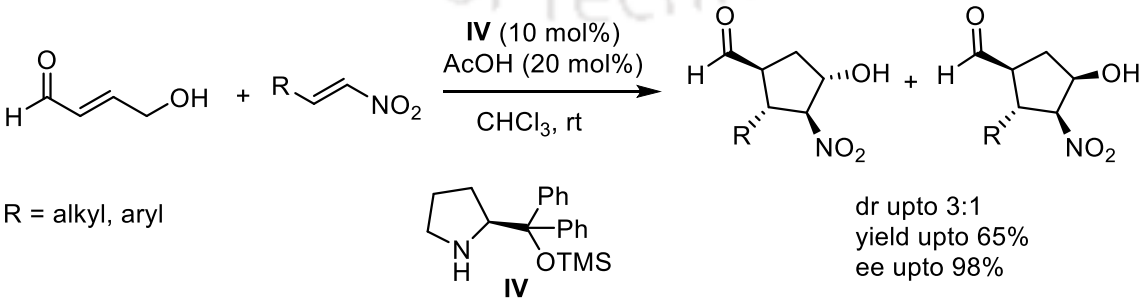
Scheme 1.3: Asymmetric synthesis of 1,3-oxazolidine

In 2012, Matsubara and co-workers also utilized *γ*-hydroxy *α,β*-unsaturated thioester as a model substrate instead of *γ*-hydroxy *α,β*-unsaturated ketone to accomplish the oxy-Michael addition reaction with aldehydes using quinidine-based thiourea catalyst **II** with good enantiomeric excess and moderate diastereoselectivities (Scheme 1.4).[19] The reaction proceeded *via* hemiacetal intermediate for the facile access of chiral acetal compounds.



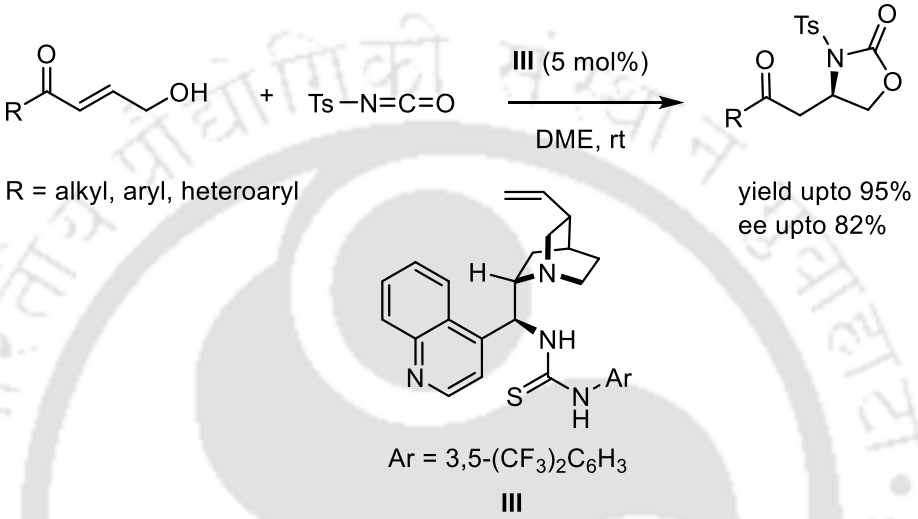
Scheme 1.4: Asymmetric synthesis of 1,3-dioxolanes using *γ*-hydroxy *α,β*-unsaturated thioester

In the same year, Hong research group[20] illustrated a simple method for the synthesis of highly enantioselective cyclopentanecarbaldehydes with four contiguous stereogenic centers. They have reported the Michael-Henry reaction between 4-hydroxy but-2-enal and nitroalkenes in the presence of proline derived catalyst **IV** *via* dienamine catalysis (Scheme 1.5).



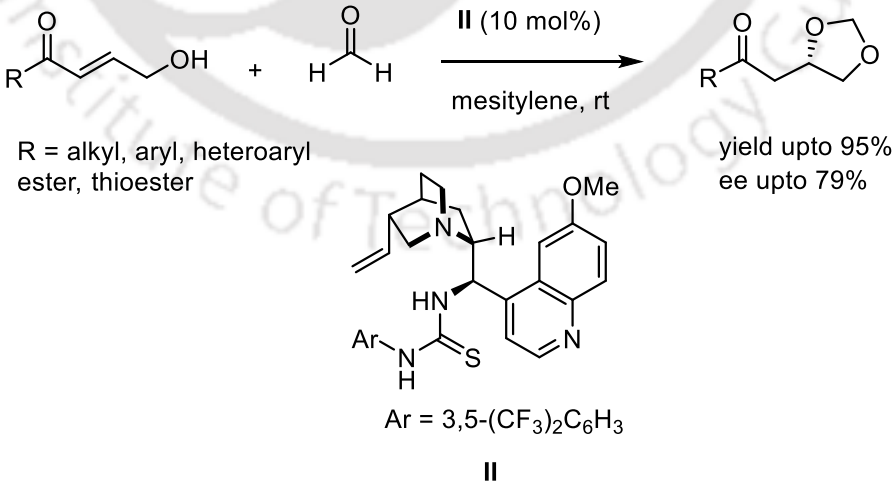
Scheme 1.5: Asymmetric synthesis of cyclopentanecarbaldehydes

Matsubara *et al.*[21] also observed that isocyanate can be used as an efficient reactant for the cycloaddition reaction. For this purpose, they have reported formal [3 + 2] cycloaddition reaction between γ-hydroxyenones and isocyanate for the construction of chiral 2-oxazolidinone *via* aza-Michael addition reaction using cinchonidine-thiourea catalyst **III** (Scheme 1.6). The stereochemistry of the product was highly dependent on the addition sequence of the starting materials and catalyst.



Scheme 1.6: Asymmetric synthesis of 2-oxazolidinone

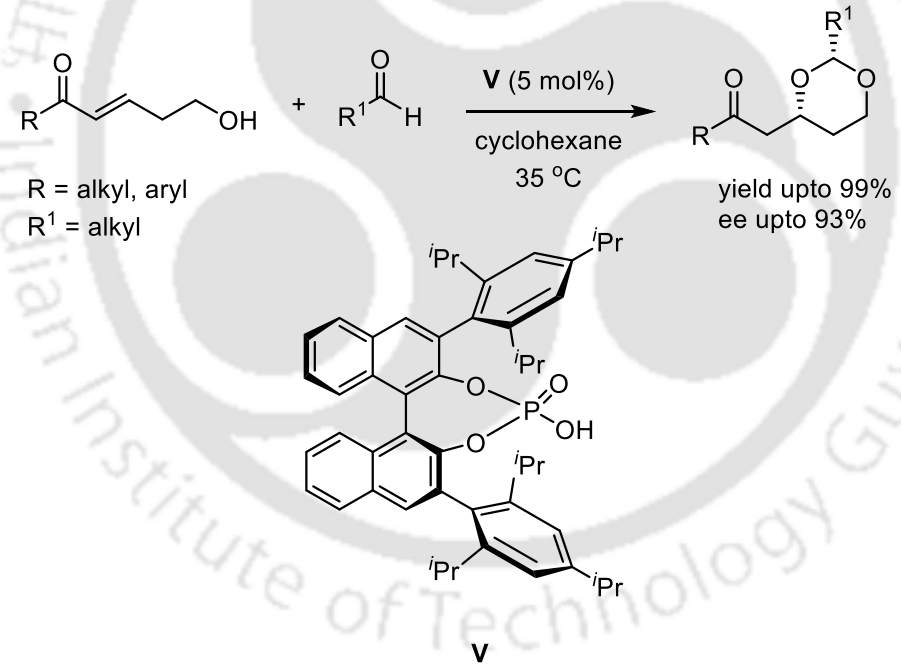
After performing the reaction between aldehydes and γ-hydroxyenones (Scheme 1.2), further, the same group developed a novel asymmetric oxy-Michael reaction with



Scheme 1.7: Asymmetric oxy-Michael reaction

formaldehyde (as an oxygen-centered nucleophile) and γ-hydroxyenones through achiral hemiacetal intermediates in the presence of quinidine thiourea catalyst **II** with moderate enantioselectivities and also avoided the mixture of diastereomers (Scheme 1.7).[22]

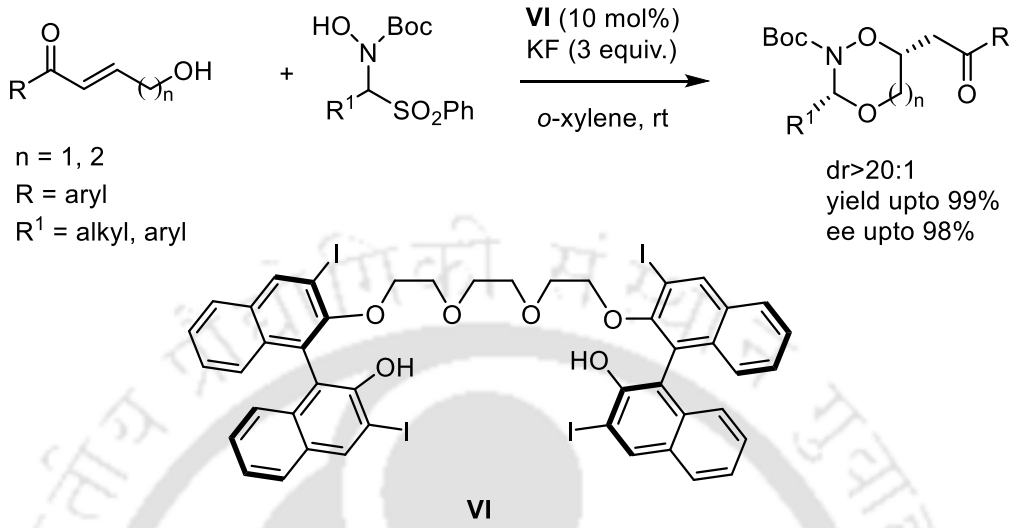
Stereoselective 1,3-dioxanes are important structural frameworks and are converted to optically active 1,3-polyol motifs found in a variety of polyketides such as amphotericin B and atorvastatin. Previously, Matsubara group reported amino-thiourea catalyzed asymmetric synthesis of 1,3-dioxolanes[17,19,22] from γ-hydroxyenones. However, amino-thiourea catalyst was not so efficient for the development of 6-membered 1,3-dioxane. Thus, the group described a chiral phosphoric acid catalyzed reaction between δ-hydroxyenones and aldehydes *via* hemiketalization followed by intramolecular oxy-Michael addition reaction to achieve the enantioselective 1,3-dioxanes with single diastereomer (Scheme 1.8).[5i]



Scheme 1.8: Chiral phosphoric acid catalyzed asymmetric oxy-Michael reaction

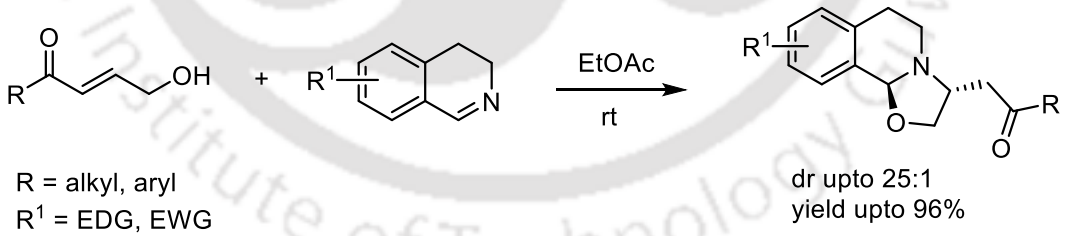
To further extension, Song *et al*. synthesized highly enantio- and diastereoselective diaxazinane and dioxazepane heterocycles by the asymmetric cycloaddition reaction between N-Boc-N-hydroxy amido sulfone (nitrone precursor) and γ,δ-hydroxyenones

using song's chiral oligo ethylene glycol **VI** as a cation binding catalyst and KF as a base to activate the catalyst (Scheme 1.9).[23]



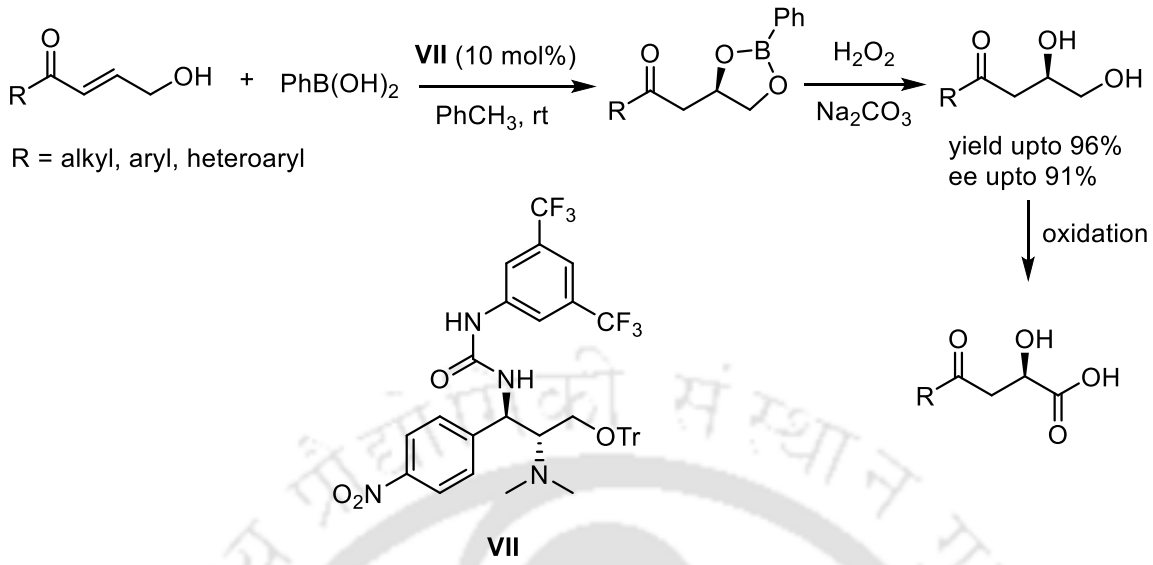
Scheme 1.9: Asymmetric synthesis of diaxazinane and dioxazepane heterocycles

A facile and convenient method for the synthesis of highly diastereoselective oxazolo[2,3-*a*]tetrahydro-isoquinolines was described by Yang and co-workers. The process was carried out *via* [3 + 2] cycloaddition reaction of *γ*-hydroxyenones and 3,4-dihydroisoquinolines under "green" conditions without using catalyst as well as additive and furnished the products with excellent yields (Scheme 1.10).[24]



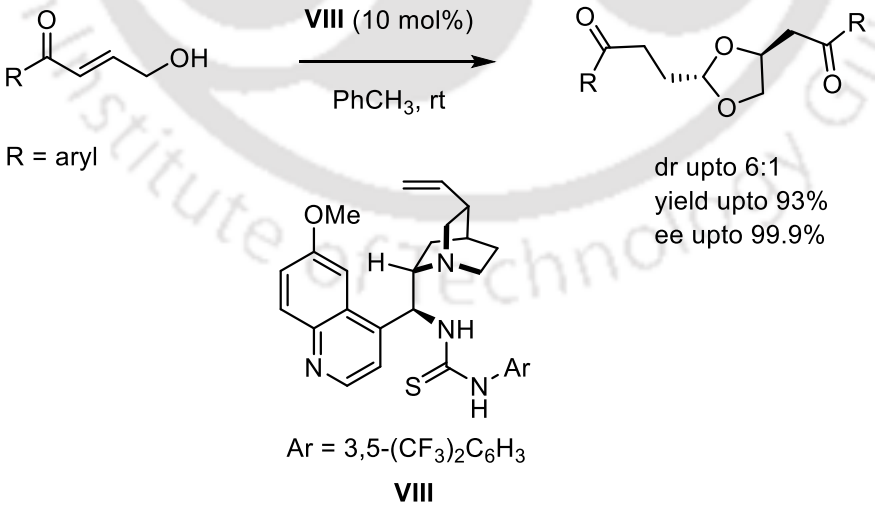
Scheme 1.10: Diastereoselective synthesis of oxazolo[2,3-*a*]tetrahydro-isoquinolines

In 2017, Chen *et al*. exploited the same protocol of Falck (Scheme 1.1) by changing the catalyst. They employed chloramphenicol based urea catalyst **VII** for the intramolecular oxy-Michael reaction between *γ*-hydroxyenones and boronic acid (Scheme 1.11).[25] The subsequent oxidation of the corresponding products furnished the *α*-hydroxy chiral compounds with moderate to good yields and high enantioselectivities.



Scheme 1.11: Chloramphenicol based urea catalyzed oxy-Michael reaction

Recently, our group[26] developed a new method for asymmetric redox isomerization followed by dimerization of *γ*-hydroxyenones to access a variety of chiral acetal compounds. These compounds were achieved under mild reaction conditions with high enantiomeric excess and moderate diastereoselectivities in the presence of quinine-derived thiourea catalyst **VIII** and theoretical investigations revealed that kinetically controlled process might occur to attain the diastereoselectivity for this reaction (Scheme 1.12).

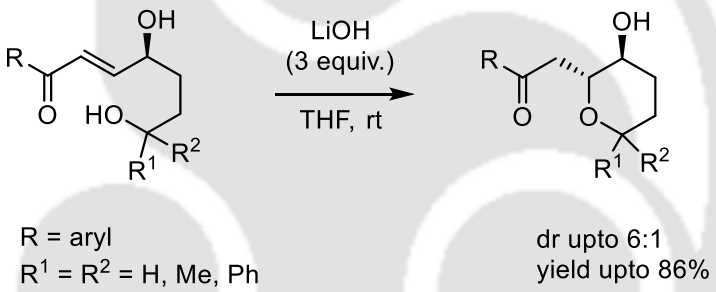


Scheme 1.12: Asymmetric synthesis of acetal *via* dimerization

B. Cyclization reaction

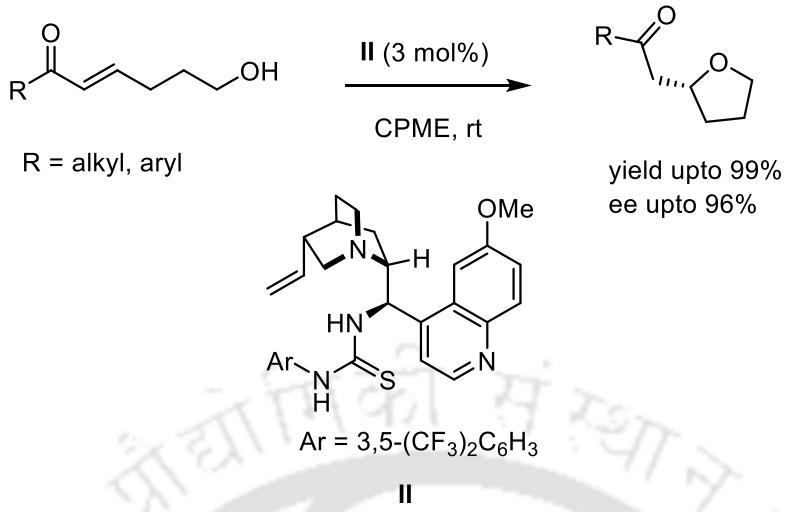
Intramolecular cyclization *via* hetero-Michael[27,28] reaction is an important alternative convenient and atom-economic method that has been used for the synthesis of different heterocyclic moieties which are important building blocks in organic synthesis and material science. In this context, a number of methods have been developed for the construction of heterocycle compounds through intramolecular cyclization reactions. Some of the examples employing terminal hydroxyenone derivatives have been documented here.

For example, Taylor group[29] reported an efficient base mediated intramolecular oxy-Michael reaction of γ-hydroxyenones containing tethered hydroxyl moiety for the synthesis of tetrahydropyran derivatives (Scheme 1.13).



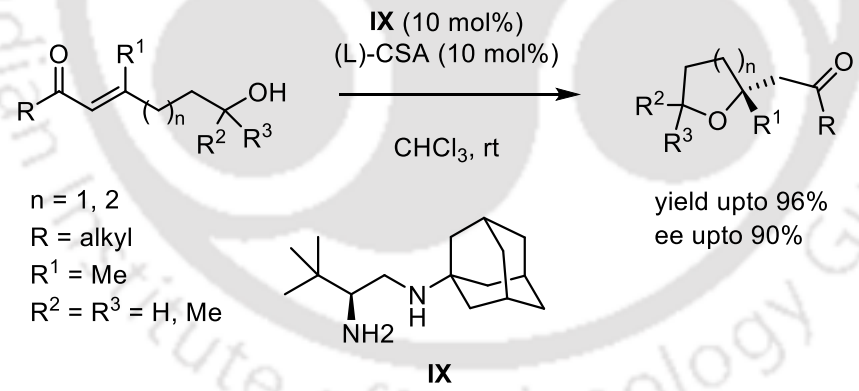
Scheme 1.13: Synthesis of tetrahydropyran

In 2011, Matsubara *et al.*[30a] reported organocatalytic asymmetric tetrahydrofuran synthesis (cyclic ether) with excellent yields and enantioselectivities from ω-hydroxyenone derivatives by using cinchona-derived bifunctional thiourea catalyst **II** (Scheme 1.14). These oxy-cyclic frameworks are present in a wide range of natural products and bioactive compounds. In this contents, the same group further illustrated the important role of H-bonding[30b] of thiourea catalyst in the reaction mechanism.



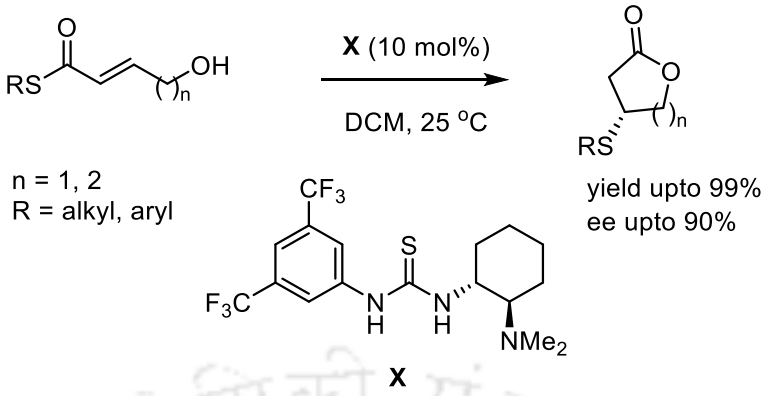
Scheme 1.14: Asymmetric synthesis of tetrahydrofuran

Later, Zhao and co-workers developed a new asymmetric method for the synthesis of tetrahydrofuran and tetrahydropyran compounds with good yields and high enantioselectivities by using dual primary and secondary amine catalyst **IX** *via* intramolecular oxy-Michael reaction of hydroxyenone derivatives (Scheme 1.15).[31]



Scheme 1.15: Organocatalytic intramolecular oxy-Michael reaction

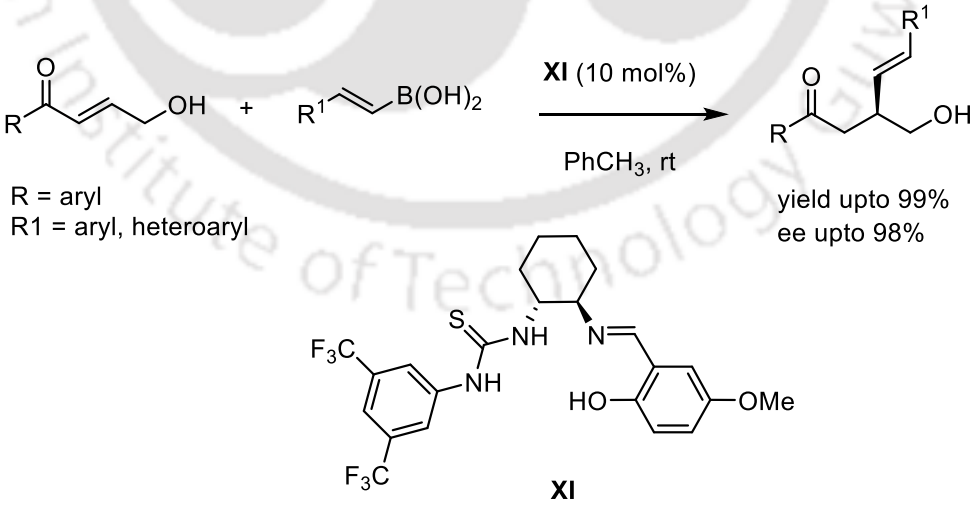
Further, Matsubara group demonstrated the access of chiral *β*-mercaptolactones *via* isomerization of *γ*-hydroxy *α*,*β*-unsaturated thioesters in the presence of cyclohexyl-derived amino thiourea catalyst **X** (Scheme 1.16).[32] The catalyst presumably activates the substrate through the simultaneous formations of covalent and non-covalent bond.



Scheme 1.16: Asymmetric synthesis of *β*-mercaptolactones

C. Michael reaction

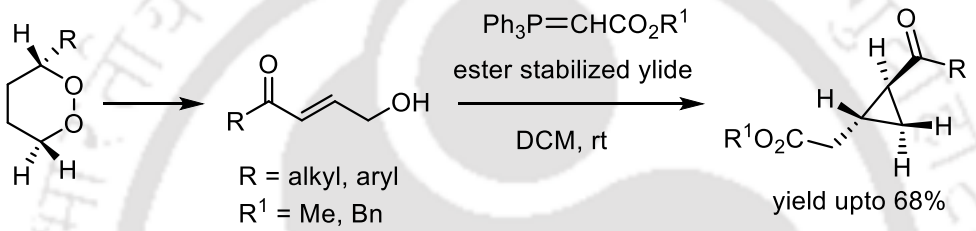
Michael reactions are also a key topic for the development of carbon-carbon and carbon-hetero bonds in organic chemistry. *γ*-Hydroxyenones were also employed in Michael reaction. Thus, Takemoto group reported[33] asymmetric Michael addition reaction between *γ*-hydroxyenones and alkenyl boronic acid with excellent yield and enantioselectivity in the presence of cyclohexyl-derived imino-thiourea catalyst **XI** (Scheme 1.17). The hydroxyl group present in the substrates have crucial role in the reaction to understand the stereochemistry of the products.



Scheme 1.17: Asymmetric alkenylation *via* Michael reaction

D. Cyclopropane ring formation

Cyclopropane ring is one of the simplest structural framework in organic chemistry and became a versatile synthetic intermediate for the synthesis of various natural products.[34] The higher ring strain of the cyclopropane ring made it easier to cleave the carbon-carbon bond compared to other cyclic compounds. A variety of methods have been reported for the synthesis of cyclopropane rings.[35] This compound was also formed from γ-hydroxyenones (*in situ* derived from 1,2 dioxines) as developed by Taylor group under mild reaction conditions using ester stabilized ylide *via* a five membered O−P intermediate (Scheme 1.18).[36]



Scheme 1.18: Cyclopropane ring formation

From the literature survey, it reveals that hydroxyenones have been utilized in different types of asymmetric and non-asymmetric reactions to attain the target molecule. Moreover, these moieties have played prominent role in organic chemistry for the synthesis of a wide range of heterocycles. Therefore, it is still required to explore a variety of methods involving hydroxyenones with suitable reactants for the construction of desired molecules. In the following chapters, we have described few new methodologies to synthesize useful frameworks using hydroxyenones.

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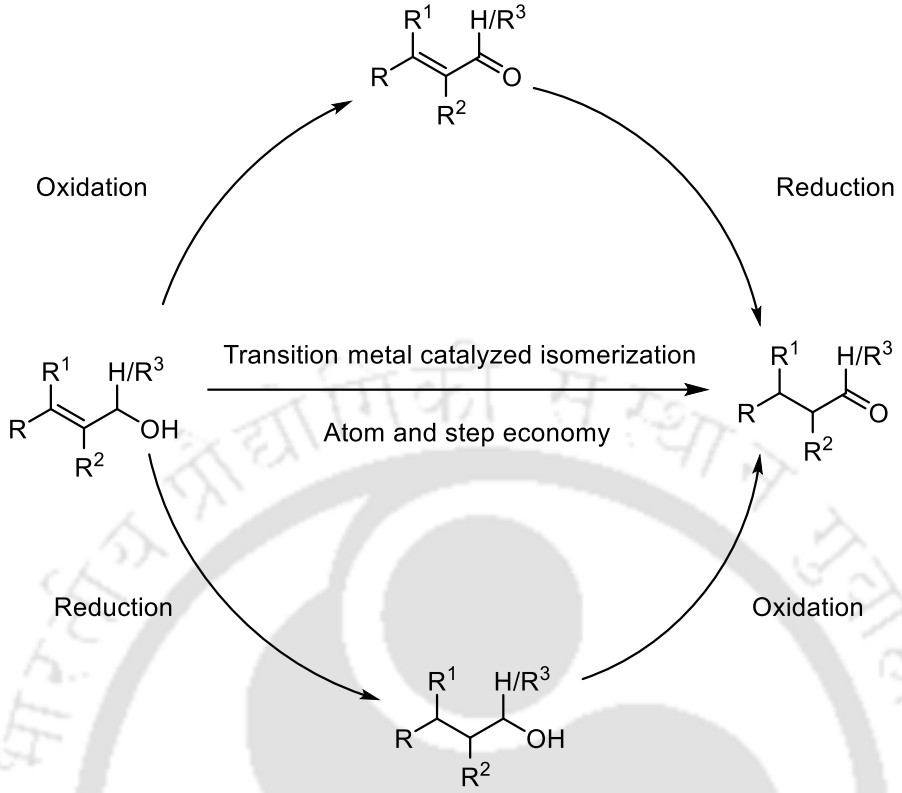
Chapter 2

Organocatalytic Redox Isomerization of Electron-Deficient Allylic Alcohols: Synthesis of 1,4-Ketoaldehydes

2.1 Introduction

One of the current challenges in organic chemistry is to develop reactions that provide products with high level of efficiency, selectivity and atom economy.[1] Isomerization reactions are considered one of the most atom economic methods as no by-products are formed during the course of the reactions.[2] Commonly, isomerization is the process in which one molecule is converted to other molecule having same molecular formula but the orientation is different (e.g. A-B-C→B-A-C). Variety of isomerization reactions have been developed till now such as i) redox isomerization ii) photoisomerization and iii) cycloisomerization. Among them, redox isomerization is an important area to access a diversity of synthetically valuable and more complex building blocks in organic chemistry. Redox isomerization is also an intrinsically efficient process as it avoided external oxidants and reductants and excluded the formation of unwanted by-products. At the end of 18th century, Joseph Priestley first discovered a redox reaction by changing the oxidation state between a metal atom and its corresponding metal ion. The term 'redox' defines in the combination of oxidation and reduction processes. These two reactions are interrelated to each other and always happen simultaneously.

In recent years, a great interest has been focused on the synthesis of 1,4-dicarbonyl compounds, since these compounds serve as useful synthons for the synthesis of various carbo- and heterocyclic structural motifs.[3,4] Although numerous procedures were known in the literature for the synthesis of 1,4-dicarbonyl compounds[5] but traditional approaches have followed multistep protocols. On the other hand, redox isomerization of readily available allylic alcohols to corresponding carbonyl compounds is an attractive and atom-economic process, which circumvents the use of highly reactive as well as expensive reagents and also reduces the number of protection-deprotection steps often required for such transformations (Scheme 2.1).[1] Transition metal complexes are also able to promote a huge number of chemo, regio, and stereoselective transformations.



Scheme 2.1: General strategy to access carbonyl compounds from allylic alcohols

2.2 General mechanism for transition metal catalyzed isomerization reaction

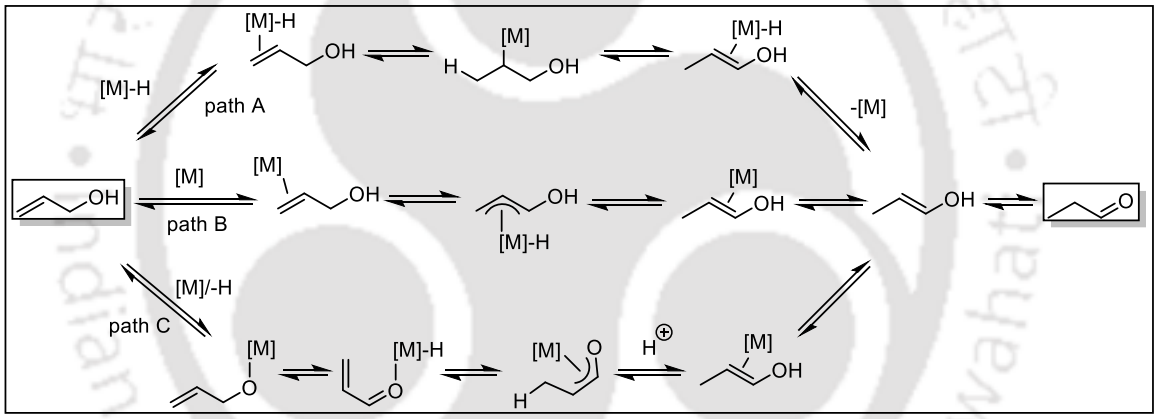
In the following discussion, three general mechanisms have been shown to explain the reaction process.[6]

(i) **The metal hydride mechanism** (Scheme 2.2, path A): In this case, π-orbitals or double bond of allyl alcohol coordinates first with the metal−hydride complex which is either isolated or generated *in situ.* Subsequent insertion of the metal hydride into the alkene moiety generated the key metal-alkyl species and then *β*-hydride elimination led to an enol and regenerated the metal hydride catalyst. Finally, tautomerization of the enol provided the corresponding carbonyl compound.

(ii) **The π-allyl mechanism** (Scheme 2.2, path B): Herein, a π-alkyl−metal complex is formed by coordination of the alkene moiety to the metal centre (which does not contain a hydride). Next formal oxidative addition of the C−H single bond of the allylic alcohol formed a π-allyl−metal hydride intermediate. After reductive elimination, the

coordinated product (enol metal complex) is formed and subsequently dissociated to the metal catalyst as well as to the free enol form. Further, tautomerization of the enol form attained the corresponding carbonyl compound.

(iii) **The intramolecular 1,3-hydrogen shift mechanism** (Scheme 2.2, path C). Normally, this mechanism is performed under basic conditions and involvement of oxygen moiety is observed. The deprotonation of allylic alcohol resulted in the initial formation of a transition metal alkoxide complex. After that, *β*-hydride abstraction from the substrate furnished an enal−metal hydride intermediate. Further, intramolecular conjugate addition of the hydride to the enal led to the formation of an oxa–allyl metal species which upon protonation released the metal catalyst as well as the free enol and finally formed the corresponding carbonyl compound *via* enol tautomerization.



Scheme 2.2: General mechanism for transition metal catalyzed isomerization of allylic alcohol

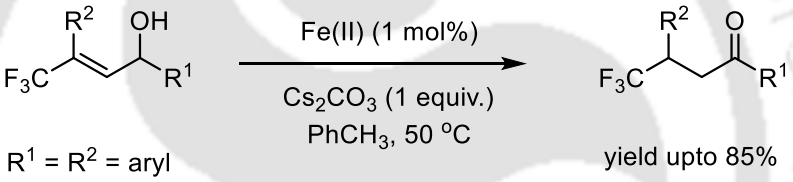
Remarkably, the third mechanism was initially proposed by Trost and Kulawiec for the redox isomerization of allylic alcohols in the presence of ruthenium catalyst.[6b] Especially, an analogous case of isomerization of allylic amines has been reported by Noyori and co-workers, and they proposed a mechanism where nitrogen atom played a key role to coordinate with the metal centre.[7] Based on the experimental evidences[8] (labelling experiments, DFT calculations) and literature survey, the above mentioned mechanism has been proposed.

2.3 Transition metal catalyzed redox isomerization reactions

Over the past decades, a variety of transition metal complexes have been widely utilized for the redox isomerization reaction[9] of readily accessible allylic alcohols to saturated carbonyl compounds which are very valuable raw materials in organic chemistry. Among them, mostly iron (Fe), ruthenium (Ru), rhodium (Rh), and iridium (Ir) complexes have been found to be suitable in the isomerization of allylic alcohols. Enormous synthetic methodologies have been reported in the literature involving transition metal catalyzed redox isomerization reaction of allylic alcohols. Some of the reported strategies have been shown in the following section (Scheme 2.3).

A. Iron-catalyzed:[10]

Cahard, 2013

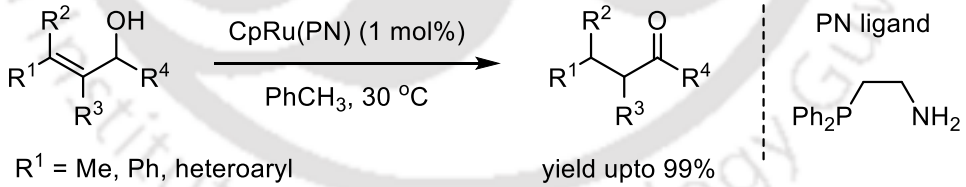


$R^1 = R^2 = aryl$

yield upto 85%

B. Ruthenium-catalyzed:[11,12]

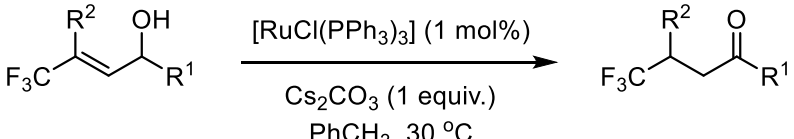
Ikariya, 2005



R^1 = Me, Ph, heteroaryl
$R^2 = R^3 = R^4$ = H, alkyl

yield upto 99%

Cahard, 2012

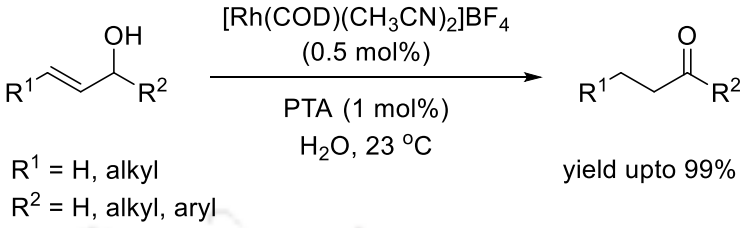


R^1 = alkyl, aryl
R^2 = H, alkyl, aryl

yield upto 99%

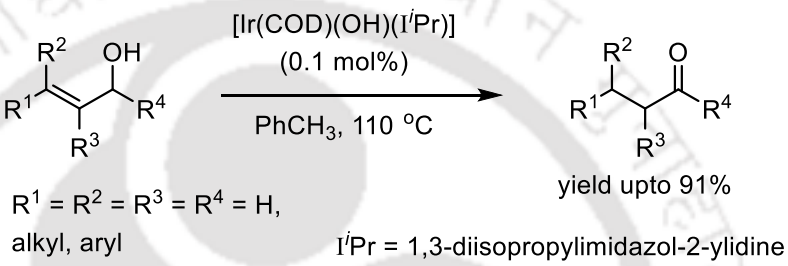
C. Rhodium-catalyzed:[13,14]

Matute, 2010



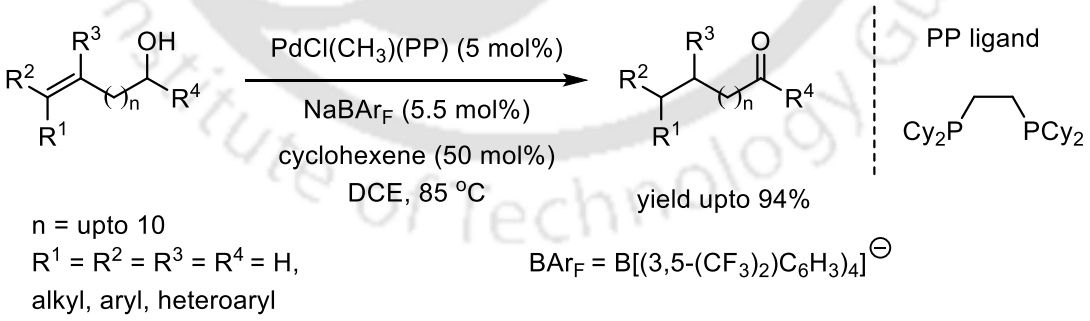
D. Iridium-catalyzed[15,16]

Nolan, 2014



Scheme 2.3: Approaches towards redox isomerization using transition metal catalysts

In 2014, as a continuation of the research on isomerization reactions, the Mazet group[17a] further revealed a well-defined palladium complex for the isomerization of highly substituted allylic, homoallylic and alkenyl alcohols (Scheme 2.4). The similar work Pd-catalyzed isomerization with double migration has been developed by Sigman and co-workers.[17b]



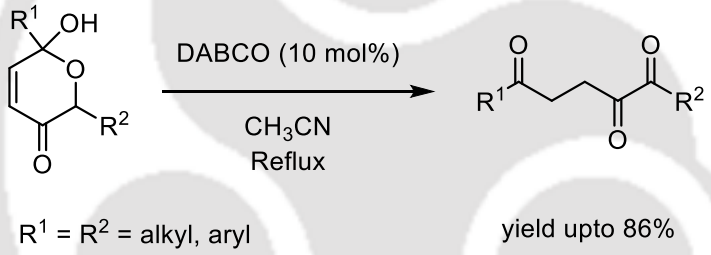
Scheme 2.4: Palladium-catalyzed redox isomerization of allylic and homoallylic alcohols

However, the harsh reaction conditions and the use of an expensive catalysts in the metal catalyzed redox isomerization limited their use for the synthesis of the desired products.

2.4 Organocatalytic redox isomerization reactions

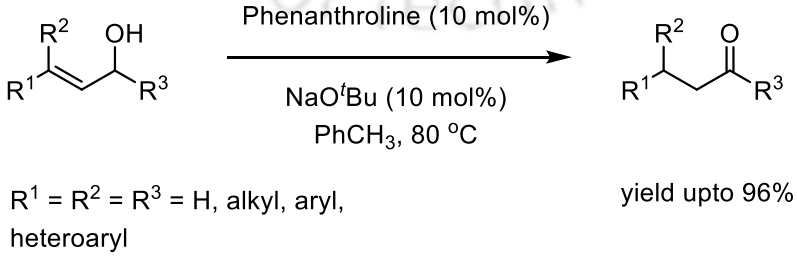
Importantly, organocatalytic redox isomerization[18,19] of allylic alcohols has been identified as an attractive alternative strategy compared to metal catalyzed redox isomerization. However, only few methods have been reported for the same. Previously, few acid and base-catalyzed redox isomerization of γ-hydroxyenones to 1,4-diketones have been reported.[20] Unfortunately, these earlier reported methods suffered from the limitations associated with narrow substrate scope, lower yields and high reaction temperature. Taylor *et al*. observed the formation of 1,4-diketones and 1,4-ketoaldehydes by using 1,2-dioxines and phosphorus ylide but lower yields (~30%) were observed for 1,4-ketoaldehydes.[21]

In 2010, Miles and co-workers revealed DABCO catalyzed isomerization of 6-hydroxy-2H-pyranones to 1,2,5-triketones with moderate to good yields (Scheme 2.5).[22]



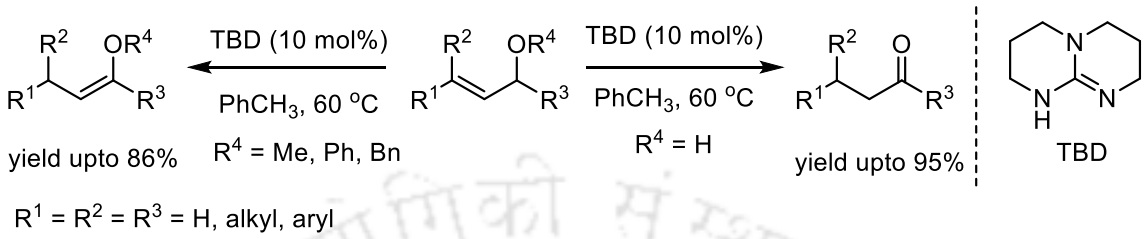
Scheme 2.5: DABCO catalyzed redox isomerization

Recently, Tang *et al*.[23] established phenanthroline-*tert*-butoxide (as a radical initiator) catalyzed transition metal free hydrogen transporting allylic isomerization for the synthesis of carbonyl compounds (Scheme 2.6) and the corresponding experimental evidences showed that the reaction proceeds *via* the radical pathway.



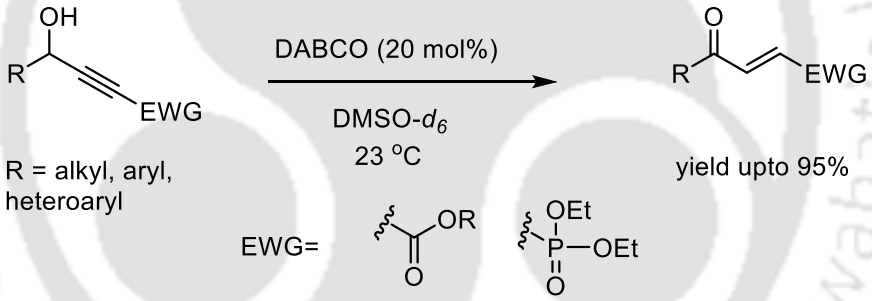
Scheme 2.6: Phenanthroline-*tert*-butoxide catalyzed redox isomerization

In 2016, a mild base (TBD) catalyzed approach for the isomerization of electron deficient allylic alcohols and ethers has been developed by Matute and co-workers (Scheme 2.7).[24]



Scheme 2.7: TBD catalyzed redox isomerization of allylic alcohols

Recently, organocatalytic redox isomerization of propargylic alcohols has emerged as one of the key strategy in organic chemistry. For this purpose, Koide *et al.*[19a] reported highly stereoselective redox isomerization of electron deficient propargylic alcohols to *(E)*-enones in the presence of DABCO catalyst (Scheme 2.8).

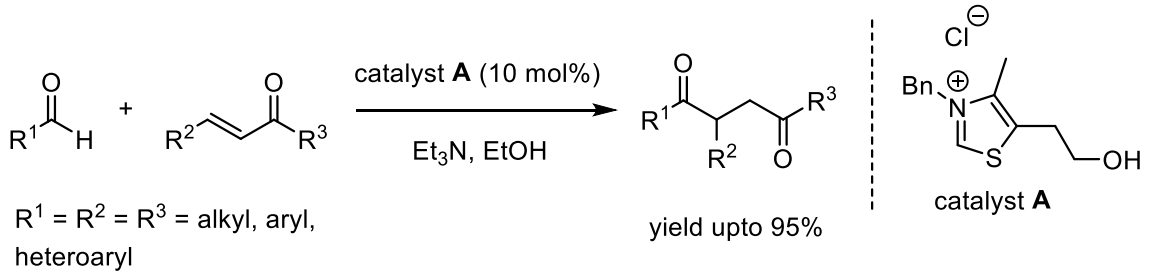


Scheme 2.8: DABCO catalyzed redox isomerization of propargylic alcohols.

2.5 Synthetic methodologies for 1,4-dicarbonyl compounds

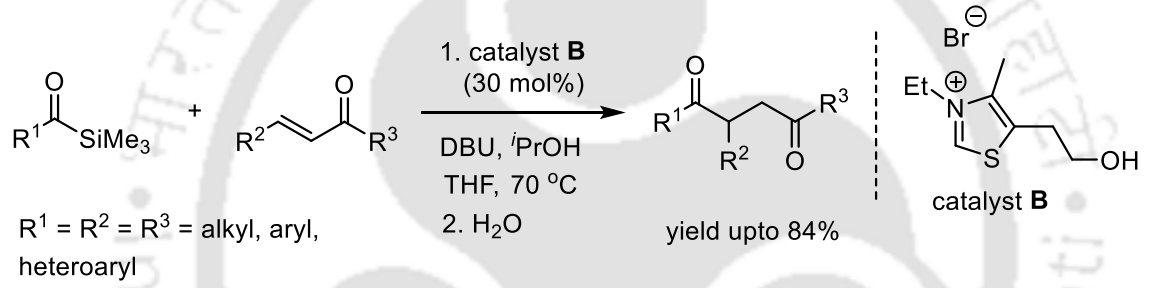
Previously, the importance of 1,4-dicarbonyl compounds in organic chemistry has been discussed in Section 2.1 and some of the selected methods have been documented in the following section.

One of the popular early reported method for the synthesis of 1,4-dicarbonyl compounds is Stetter reaction,[25] which is an umpolung chemical reaction where aldehyde is converted from electrophile to nucleophile by using thiazolium salt as catalyst (Scheme 2.9).



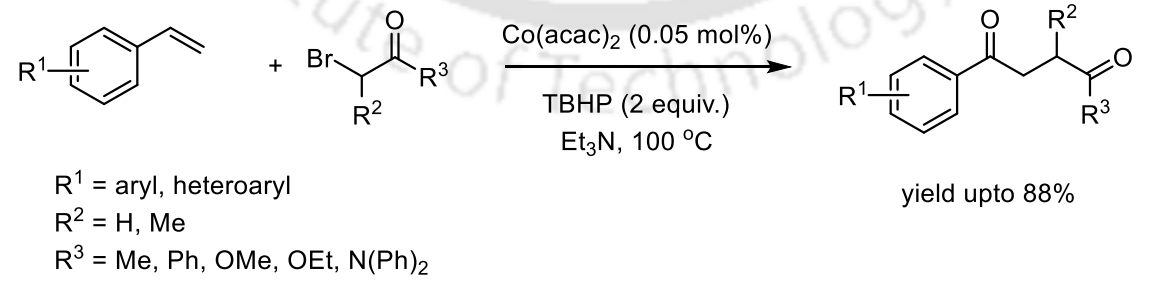
Scheme 2.9: Stetter reaction for the synthesis 1,4-dicarbonyl compounds

Further, the extension of Stetter reaction was developed by Karl Scheidt and co-workers. This group reported the conjugated addition of acylsilane to unsaturated ketones and esters for the synthesis of 1,4-dicarbonyl compounds using thiazolium salt as catalyst (Scheme 2.10).[26]



Scheme 2.10: Synthesis of 1,4-dicarbonyl compounds

In 2014, Wan *et al.*[27] demonstrated cobalt catalyzed reaction between easily available styrene and *α*-bromo carbonyl compounds for the construction of 1,4-dicarbonyl derivatives with a wide range of substrate scope. This protocol is quite simple compared to the other previous approaches (Scheme 2.11).



Scheme 2.11: Cobalt catalyzed synthesis of 1,4-dicarbonyl compounds

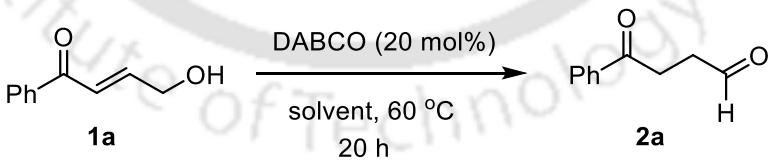
2.6 Result and discussion

Realizing the potential of redox isomerization and 1,4-ketoaldehydes as an important building blocks, a redox isomerization strategy for the synthesis of 1,4-ketoaldehydes from γ-hydroxyenones was envisaged. In fact, the drawbacks associated with the use of excess base and lower yields of the products as reported by Taylor *et al.*,[21] restricted the use of the above-mentioned organo catalyzed redox isomerization. To circumvent this problem, we have developed a new strategy for the synthesis of 1,4-ketoaldehydes, the details of which are discussed as follows.

Initially, the investigation was started by stirring 3-benzoylprop-2-en-1-ol (**1a**) as a model substrate with DABCO (20 mol%) catalyst in DCE at 60 °C for 20 h (Table 1). The product was isolated as **2a** with 78% yields (Table 1, entry 1) and characterized by NMR, IR and HRMS analysis. The catalytic amount of base was sufficient to produce 1,4-dicarbonyl compound in good quantity. To improve the yield of the product, different solvents were screened under similar reaction conditions. It was found that toluene and acetonitrile produced more than 70% yield (Table 1, entries 2-3). Moderate yields were observed in case of THF and dioxane solvent (Table 1, entries 4-5). Further optimization was performed in DMF and DMSO solvent and both provided higher yields, 82% and 93% respectively (Table 1, entries 6-7).

Optimization of reaction condition

Table 1: Solvent screening



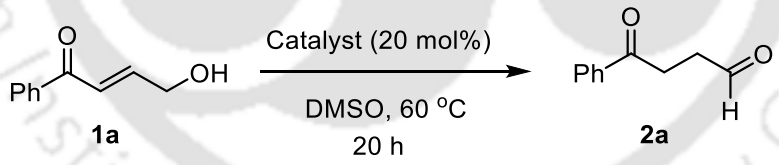
entry[a]	solvent	yield (%)[b]
1	DCE	78
2	Toluene	74
3	CH_3CN	75

4	THF	63
5	Dioxane	70
6	DMF	82
7	DMSO	93

[a]Reaction conditions: All reactions were carried out with compound **1a** (0.2 mmol) in 1 mL solvent; [b]Isolated yield after silica gel column chromatography.

It was observed from Table 1. that higher polar solvent is more efficient to produce the isomerized product. Hence, DMSO was chosen as the best solvent for the reaction and further experiments were carried out in DMSO using various organic base catalysts and the results are summarized in Table 2. As can be seen, 1,8-diazabicyclo [5.4.0]- undec-7-ene (DBU) could not promote the isomerization reaction after 20 h due to lower nucleophilicity (steric and resonance factor) of the catalyst (Table 2, entry 2). Inferior yields 45% and 52% of the isomerized product 3-benzoylpropanal (**2a**) were obtained with Et_3N and DIPEA respectively (Table 2, entries 3-4). However, 1,1,3,3-tetramethylguanidine (TMG), pyridine, and the inorganic base such as potassium carbonate (K_2CO_3) failed to promote under identical conditions (Table 2, entries 5−7).

Table 2. Catalyst and Temperature Screening



entry[a]	catalyst (%)	yield (%)[b]
1	DABCO	93
2	DBU	0
3	Et_3N	45
4	DIPEA	52
5	TMG	0
6	Pyridine	0

7	K_2CO_3	0
8	DMAP	71
9[c]	DABCO	95
10[d]	DABCO	89
11[e]	DABCO	67

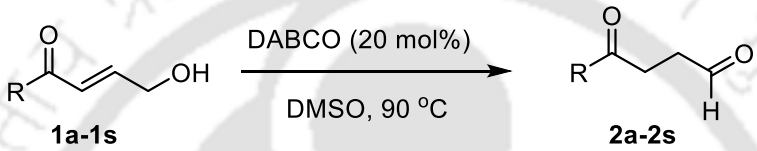
[a]Reaction conditions: 0.2 mmol of **1a** in 1 mL of solvent using 20 mol% of catalyst. [b]Isolated yield after silica gel column chromatography. [c]Reaction performed at 90 °C for 5 h. [d]10 mol% catalyst was used at 90 °C for 5 h. [e]Reaction performed at 120 °C for 5 h.

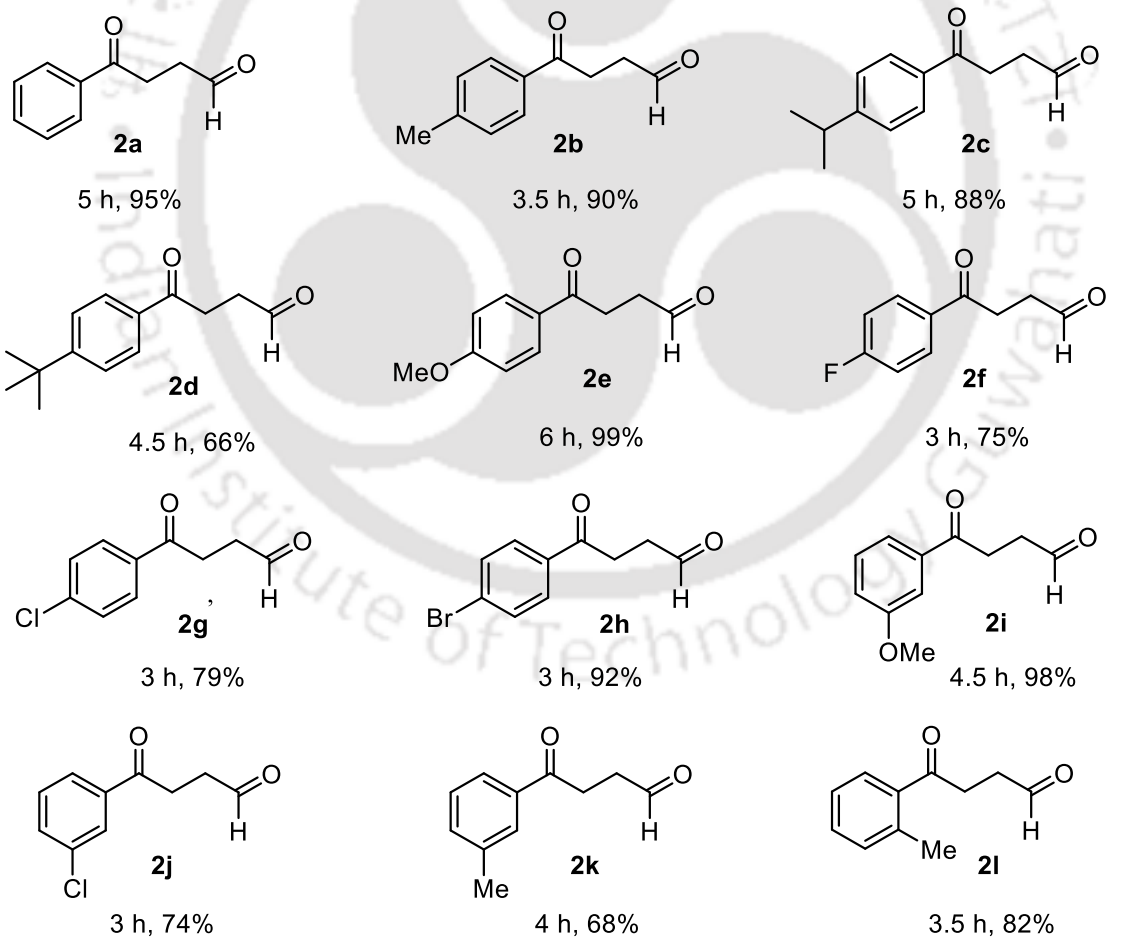
DMAP was also found to be less effective than DABCO (Table 2, entry 8). The yield was further enhanced to 95% by performing the reaction at higher temperature (90 °C) and the reaction time was shortened prominently (Table 2, entry 9). A lower yield (89%) was observed with 10 mol% of the catalyst (Table 2, entry 10). Also, further increase in temperature (120 °C) is not favourable for the reaction (Table 2, entry 11). Hence, 20 mol% of DABCO catalyst in DMSO solvent at 90 °C was found to the best conditions (based on the higher yield of the product) for the progress of the reaction (Table 2, entry 9).

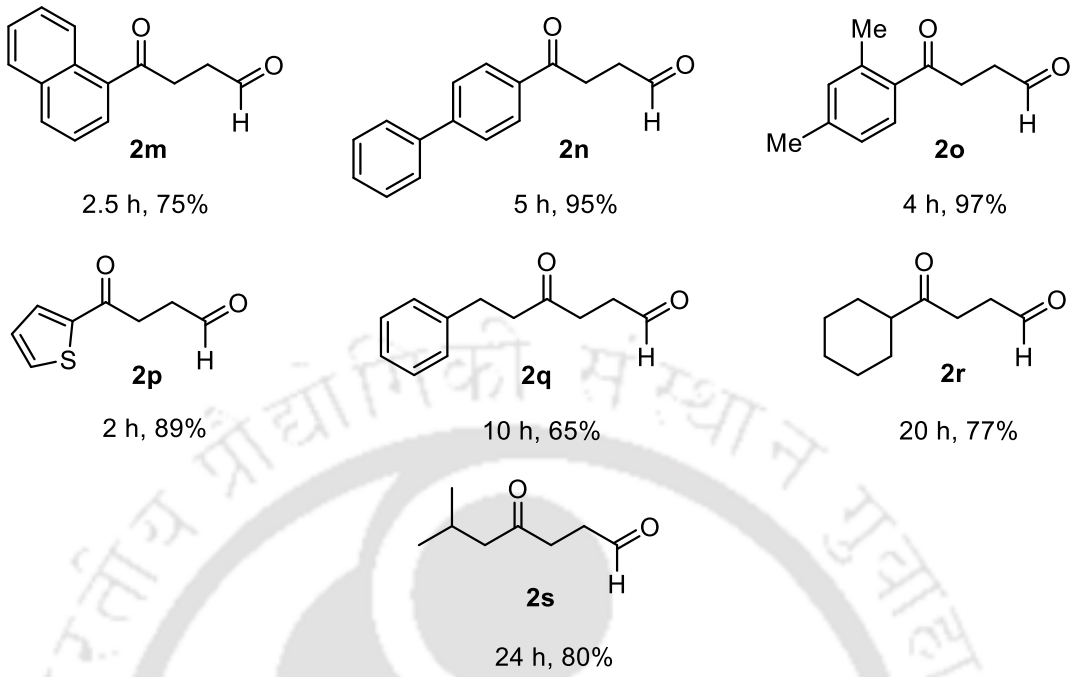
2.7 Substrate scope

With the optimized conditions in hand, the scope and generality of the reaction was ventured. Initially, different *γ*-hydroxy aryl enones were prepared and treated under the reaction conditions (Scheme 2.12). It turned out that the reaction is quite general for a variety of electron-rich and electron-poor aryl enones. Substitutions at the *ortho*, *para*, and *meta* positions of the phenyl ring were also well tolerated. 4-Methyl-substituted aryl enone provided 90% yield of the product **2b**. A similar yield was observed with 4-*iso*-propyl-substituted aryl enone **1c**, but a lower yield was obtained with 4-*tert*-butyl-substituted aryl enone **1d**. Consequently, 4-methoxy-substituted aryl enone **1e** was found to be the best substrate, providing the product **2e** in 99% yield. Then, 4-halo-substituted aryl enones were examined under the reaction conditions, and the desired products were obtained in acceptable yields. 4-Fluoro and 4-chloro-substituted enones **1f** and **1g**

resulted similar yields 75% and 79% respectively while 4-bromo-substituted enone **1h** afforded an enhanced yield of 92%. Aryl enones having *meta*-substitutions were then prepared and subjected to the reaction conditions. Excellent yield (98%) was obtained with 3-methoxyaryl enone **1i**. 3-Chloro- and 3-methyl-substituted aryl enones afforded products **2j** (74%) and **2k** (68%) in moderate yields. Interestingly, *ortho*-substitution on the aryl group did not change the outcome of the reaction, and a good yield of 82% was attained with 2-methyl-substituted aryl enone **1l**. 1-Naphthyl-substituted enone **1m** was also engaged in the reaction, and a good yield of 75% was achieved for the desired product **2m**.







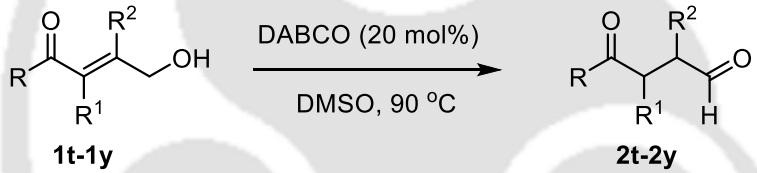
[a]Reaction conditions: 0.2 mmol of **1** in 1 mL of solvent using 20 mol% of DABCO. [b]Isolated yield after silica gel column chromatography.

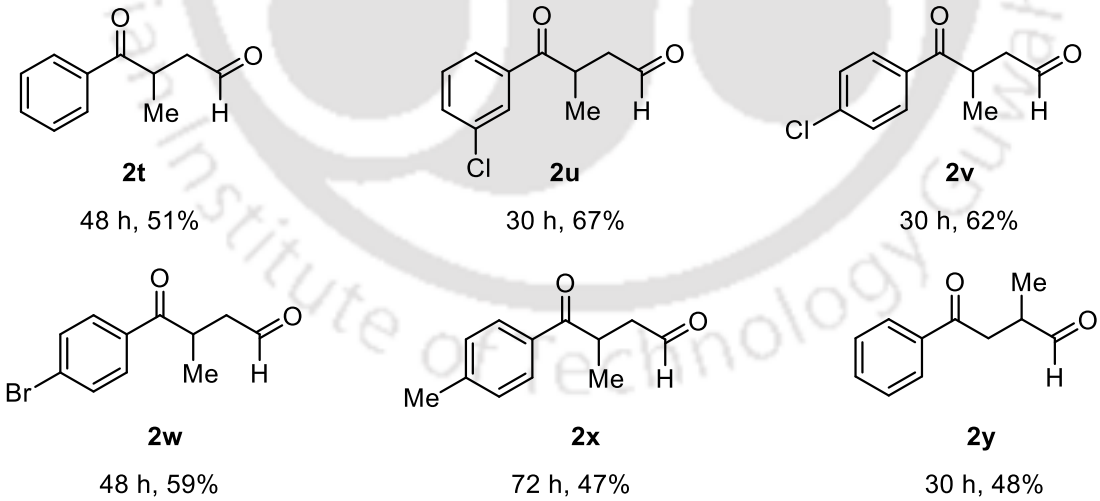
Scheme 2.12: Substrate scope of α-unbranched enones[a,b]

4-Biphenyl-substituted enone **1n** provided product **2n** in a much higher yield of 95%. Interestingly, 2,4-dimethylphenyl-substituted keto aldehyde **2o** was obtained with 97% yield after the treatment of the corresponding enone. Then, a heteroaromatic group was also incorporated in the enone moiety, and the product **2p** was isolated with 89% yield. In addition, aliphatic enones were examined under the reaction conditions, and gratifyingly, the promising results were obtained in good yields albeit longer reaction times were required. Enone **1q** having hydrocinnamyl moiety provided product **2q** with 65% yield, whereas a higher yield of 77% was achieved for the cyclohexyl-substituted product **2r**. Finally, enone **1s** having an isovaleryl moiety was tested in our reaction, and a good yield of 80% was obtained.

The next phase of experiments concerned the preparation and screening of different α,β-substituted enones to understand the electronic effect of substituents in the reaction. After performing some experiments, it was found that the α-methyl group could be tolerated in

this reaction. Thus, a variety of α-methyl enones (**1t**−**1x**) was prepared and engaged in the reaction (Scheme 2.13). In general, longer reaction times were required for significant conversion to the products. Product **2t** was isolated with 51% yield after 48 h. Substitutions at the *meta* and *para* positions of the aryl group did not alter the fate of the reaction. Moderate yields of 67% and 62% were achieved for 3- and 4-chloro-substituted aryl ketoaldehydes **2u** and **2v**. Product **2w** having a 4-bromo-substituted aryl group was isolated with a similar 59% yield. 4-Methyl-substituted aryl ketone **1x** was found to undergo isomerization slowly, and product **2x** was attained with 47% yield after 72 h. This indicates that electron deficiency of the double bond is important for the rate of the reaction for α-substituted substrates. Pleasingly, our method is also applicable for β-methyl-substituted enones such as **1y**, providing a moderate yield of 48% for the product **2y** (Scheme 2.13). From these investigations, it was revealed that unbranched enones have provided superior results compared to branched enones.





[a]Reaction conditions: 0.2 mmol of **1** in 1 mL of solvent using 20 mol% of DABCO. [b]Isolated yield after silica gel column chromatography.

Scheme 2.13: Substrate scope of α- and β-branched enones[a,b]

2.8 Plausible reaction mechanism

To understand the mechanism of our reaction, kinetic experiments were performed using **1a** in DMSO-d_6 at 90 °C with different mol% of DABCO catalyst (10, 20, and 40 mol%), and the conversions of the reaction were determined by ^{1}H NMR spectroscopy (Figure1a,b). Then, time *vs* % of conversion with different catalyst loading was plotted shown in figure 1a and that helped to determine the initial rate of the reaction. Next, ln(Initial Rate) of the reaction *vs* ln[DABCO] with different mol% of catalyst was plotted in figure 1b. From this experiments, the rate of the reaction was found to be second order overall (Figure 1a) and first order with respect to DABCO (Figure 1b). Thus, the rate-determining step involves one molecule of **1** and one molecule of DABCO in the transition state.

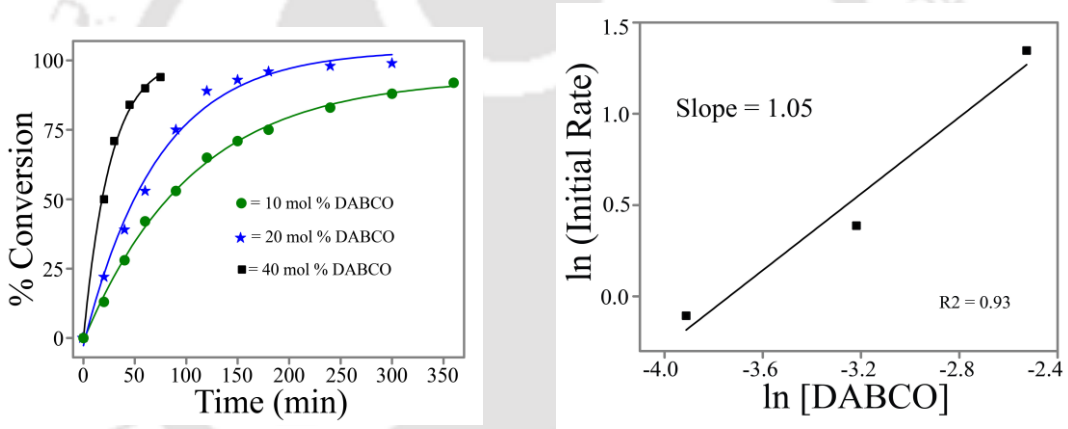
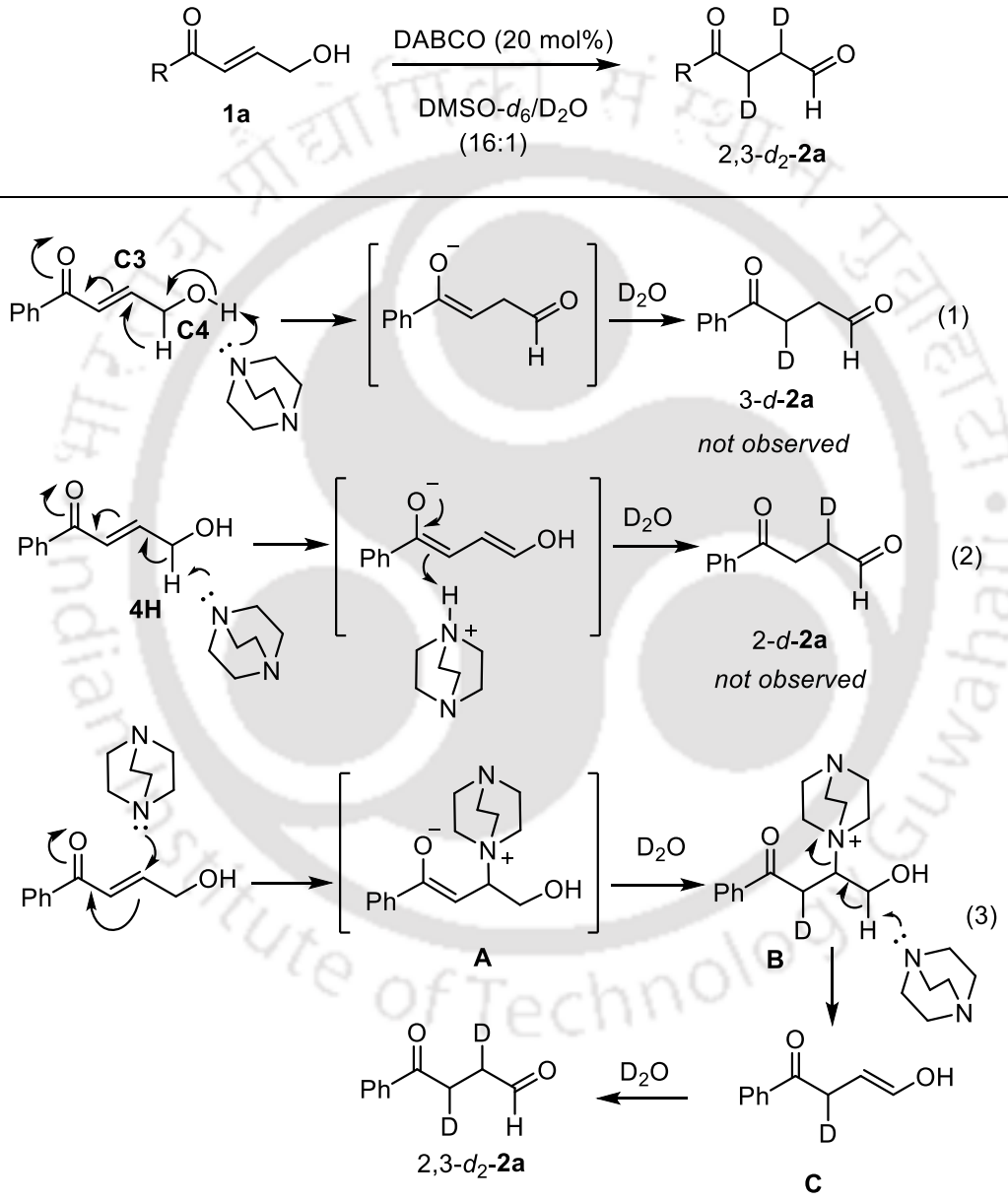


Figure 1a (Left): %Conversion *vs* Time, **Figure 1b (Right):** ln(Initial Rate) *vs* ln [DABCO]

To gain further insight into the mechanism of our redox isomerization reaction, deuterium incorporation experiment was performed with **1a**. After treatment of **1a** with 20 mol% of DABCO in DMSO-d_6/D_2O (16:1),[19b] the exclusive formation of *2,3-*d_2-**2a** was observed and confirmed by NMR as well as HRMS analysis (Scheme 2.14).[28] On the basis of experimental evidences and literature survey, a plausible mechanism has been proposed shown in Scheme 2.14. Deuterium labelling experiment eliminated the possibility of 1,2-hydride shift from C4 to C3 induced by the 4-OH deprotonation by DABCO as in this case, product *3-d-***2a** was formed (Scheme 2.14, eq. 1). Similarly, any

mechanism involving the abstraction of 4-H of **1a** by DABCO was also ruled out since in this case the resulting enolate could be quenched by more acidic protonated DABCO (pKa = 9 in DMSO) than H_2O (or D_2O; pKa = 32 for H_2O in DMSO),[19b,29] which was found to operate in the isomerization of secondary propargylic alcohol[19b] (Scheme 2.14, eq. 2).



Scheme 2.14: Proposed mechanistic pathway

Thus, the remaining possibility was the conjugate addition by DABCO to the enone to generate intermediate **A** (Scheme 2.14, eq. 3). After quenching with D_2O, the intermediate **A** converted to intermediate **B**. An E2 elimination of DABCO from **B** assisted by the general base catalysis of another molecule of DABCO led to the formation of enol **C**, which then tautomerized after abstracting a proton from residual H_2O or a deuterium from D_2O to afford *2,3-d_2*-**2a**. This pathway was matched with our desire product and consequently, it is the plausible mechanism for the isomerization products.

In summary, we have developed a facile synthesis of 1,4-ketoaldehydes by redox isomerization strategy. DABCO was found to be the best catalyst for this purpose. This method is operationally simple, convenient and the reaction conditions are amenable to scale-up. The 1,4-ketoaldehyde motifs are difficult to obtain, and our method may be very useful in the synthesis of various natural products and also may have application in drug discovery.

2.9 Experimental section

General information

All reactions were carried under air using oven dried glassware and magnetic stirring. Organic solvents were dried over anhydrous Na_2SO_4 and concentrated in a rotary evaporator under reduced pressure. For column chromatography, silica gel (60-120 mesh size) was used. For TLC analysis precoated silica gel plates were used.

^1H, ^{13}C NMR spectroscopy: 400 MHz (at 298 K) and 600 MHz. Chemical shifts (δ) were reported in ppm relative to TMS δ (^1H) 0.0 ppm, δ (^{13}C) 0.0 ppm) which was used as the inner reference with multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet). Otherwise the solvents residual proton resonance and carbon resonance ($CHCl_3$, δ (^1H) 7.26 ppm, δ (^{13}C) 77.23 ppm were used for calibration. IR spectra were recorded on an FT-IR Instrument at normal temperature by making KBr pellet and grinding the sample with KBr (IR Grade). Mass spectra were recorded on a Q-TOF mass spectrometer. Melting points were measured with Mel-Tem capillary melting point apparatus.

A. General procedure for the synthesis of *α*-unbranched *trans*-*γ*- hydroxyenones 1a-1s

α-Unbranched *trans*-*γ*-hydroxyenones were prepared according to the reported procedure.[30]

To a stirred solution of $SnCl_2 \cdot 2H_2O$ (1.5 equiv.) and KI (3 equiv.) in H_2O (25 mL), allyl bromide (1.5 equiv.), aldehydes (5 mmol) and saturated aqueous NH_4Cl solution (10 mL) were added subsequently and the resulting solution was stirred for 5 h at room temperature to obtain the homoallylic alchol. *β*,*γ*-Unsaturated ketone was achieved by PCC (1.5 equiv.) oxidation. Then *β*,*γ*-epoxy ketone was prepared from *β*,*γ*-unsaturated ketone using *m*-CPBA (1.1 equiv.). Finally, ring opening was performed to afford the title products.

B. General procedure for the synthesis of *α*-branched *trans*-*γ*- hydroxyenones 1t-1y

α-Branched *trans*-*γ*-hydroxyenones were prepared according to the reported procedure.[31]

To a stirred solution of the appropriate stabilized keto ylide (1.2 mmol) in THF (5 mL), glycoaldehyde dimer (1 mmol) was added, and the resulting solution was heated under

reflux for 3 h. The solution was cooled and the solvent was evaporated in *vacuo*. The product was purified by silica gel column chromatography.

Ylides were prepared by reacting the appropriate haloalkanone with triphenylphosphine and deprotonating with 2 N NaOH solution.[32,33]

C. General procedure for the synthesis of products 2a-2y

In a 10 mL round-bottom-flask, compound **1** (0.2 mmol) and DABCO (20 mol%) were taken and 1 mL of DMSO solvent was added to it. The round bottom flask was sealed with a glass stopper and placed on a heating block at 90 °C. After completion of the reaction, as determined by TLC, the reaction mixture was allowed to cool at room temperature and diluted with EtOAc. The organic layer was washed with water and brine and dried (Na_2SO_4). The solvents were concentrated in *vacuo* and purified by silica gel column chromatography (15% EtOAc/hexane) to afford the title compound **2**.

2.10 References

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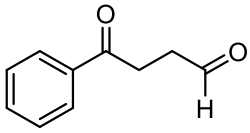
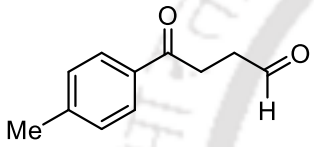
2.11 Characterization data of products

4-Oxo-4-phenylbutanal (2a)



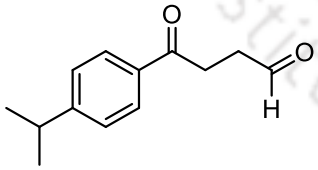
This compound was prepared according to the general procedure C. Reaction was completed after 5 h. Analytical TLC on silica gel using 15% ethyl acetate/hexane. Brown liquid (31 mg, yield: 95%); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 9.91 (s, 1H), 7.99 (d, *J* = 7.2 Hz, 2H), 7.58 (t, *J* = 7.2 Hz, 1H), 7.47 (t, *J* = 4.8 Hz, 2H), 3.33 (t, *J* = 6.3 Hz, 2H), 2.94 (t, *J* = 6.3 Hz, 2H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 200.8, 198.0, 136.7, 133.6, 128.9, 128.3, 37.9, 31.3; **FT-IR (thin film):** 1716, 1685, 1597, 1449, 1364, 1240, 983, 759, 691 cm^{-1}; **HRMS (+APCI):** Calcd for $C_{10}H_{11}O_2$ $[M + H]^+$ 163.0754; found: 163.0748.

4-Oxo-4-p-tolylbutanal (2b)



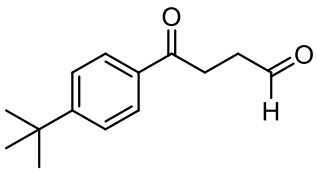
This compound was prepared according to the general procedure C. Reaction was completed after 3.5 h. Analytical TLC on silica gel using 15% ethyl acetate/hexane. Brown solid (32 mg, yield: 90%); **Mp:** 45-47 ºC; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.91 (s, 1H), 7.89 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 3.31 (t, *J* = 6.4 Hz, 2H), 2.93 (t, *J* = 6.6 Hz, 2H), 2.42 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 200.9, 197.6, 144.3, 134.2, 129.5, 128.4, 37.8, 31.1, 21.9; **FT-IR (thin film):** 1709, 1681, 1607, 1382, 1239, 1182, 977, 875, 814, 548 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{11}H_{13}O_2$ $[M+H]^+$ 177.0910; found: 177.0908.

4-(4-Isopropylphenyl)-4-oxobutanal (2c)



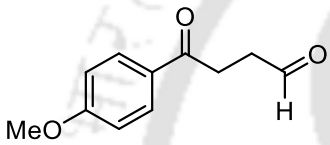
This compound was prepared according to the general procedure C. Reaction was completed after 5 h. Analytical TLC on silica gel using 15% ethyl acetate/hexane. Yellow oil (36 mg, yield: 88%); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.91 (s, 1H), 7.92 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 3.31 (t, *J* = 6.4 Hz, 2H), 2.95 – 3.00 (m, 1H), 2.93 (t, *J* = 6.4 Hz, 2H), 1.27 (d, *J* = 6.8 Hz, 6H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 200.9, 197.7, 155.1, 134.5, 128.5, 126.9, 37.8, 34.4, 31.1, 23.8; **FT-IR (thin film):** 1722, 1685, 1607, 1460, 1419, 1362, 1243, 1182, 1055, 981, 830 cm^{-1}; **HRMS (+APCI):** Calcd for $C_{13}H_{17}O_2$ $[M+H]^+$ 205.1223; found: 205.1213.

4-(4-Tert-butylphenyl)-4-oxobutanal (2d)



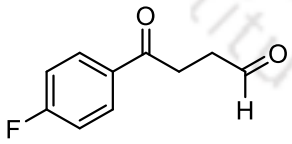
This compound was prepared according to the general procedure C. Reaction was completed after 4.5 h. Analytical TLC on silica gel using 10% ethyl acetate/hexane. Brown liquid (29 mg, yield: 66%); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.90 (s, 1H), 7.93 (d, *J* = 8.0 Hz, 2H), 7.48 (d, *J* = 8.0 Hz, 2H), 3.31 (t, *J* = 6.2 Hz, 2H), 2.92 (t, *J* = 6.2 Hz, 2H), 1.34 (s, 9H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 201.1, 197.7, 157.3, 134.0, 128.2, 125.8, 37.8, 35.3, 31.3, 31.1; **FT-IR (thin film):** 1720, 1682, 1605, 1407, 1364, 1247, 1192, 1108, 1018, 986, 828 cm^{-1}; **HRMS (+APCI):** Calcd for $C_{14}H_{19}O_2$ $[M+H]^+$ 219.1380; found: 219.1372.

4-(4-Methoxyphenyl)-4-oxobutanal (2e)



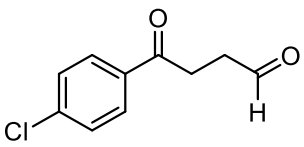
This compound was prepared according to the general procedure C. Reaction was completed after 6 h. Analytical TLC on silica gel using 18% ethyl acetate/hexane. Pale yellow oil (38.5 mg, yield: 99%); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 9.91 (s, 1H), 7.97 (d, *J* = 9.0 Hz, 2H), 6.94 (d, *J* = 9.0 Hz, 2H), 3.87 (s, 3H), 3.28 (t, *J* = 6.3 Hz, 2H), 2.91 (t, *J* = 6.3 Hz, 2H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 201.1, 196.5, 163.9, 130.6, 129.7, 114.0, 55.7, 37.9, 30.9; **FT-IR (thin film):** 1720, 1675, 1601, 1575, 1511, 1419, 1363, 1246, 1212, 1171, 1028, 834 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{11}H_{13}O_3$ $[M+H]^+$ 193.0859; found: 193.0857.

4-(4-Fluorophenyl)-4-oxobutanal (2f)



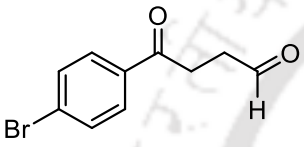
This compound was prepared according to the general procedure C. Reaction was completed after 3 h. Analytical TLC on silica gel using 12% ethyl acetate/hexane. Colorless oil (27 mg, yield: 75%); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 9.89 (s, 1H), 8.00 (dd, *J* = 5.1, 8.7 Hz, 2H), 7.13 (t, *J* = 8.7 Hz, 2H), 3.28 (t, *J* = 6.3 Hz, 2H), 2.92 (t, *J* = 6.3 Hz, 2H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 200.7, 196.4, 166.0 (d, *J* = 103.4 Hz), 133.1 (d, *J* = 3 Hz), 130.9 (d, *J* = 9.3 Hz), 115.9, 37.8, 31.1; **FT-IR (thin film):** 1721, 1685, 1597, 1506, 1410, 1363, 1233, 1209, 1158, 986, 838 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{10}H_{10}FO_2$ $[M+H]^+$ 181.0659; found: 181.0660.

4-(4-Chlorophenyl)-4-oxobutanal (2g)



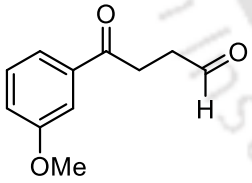
This compound was prepared according to the general procedure C. Reaction was completed after 3 h. Analytical TLC on silica gel using 12% ethyl acetate/hexane. Brown solid (31 mg, yield: 79%); **Mp:** 51-53 °C; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 9.90 (s, 1H), 7.92 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 8.4 Hz, 2H), 3.28 (t, *J* = 6.3 Hz, 2H), 2.94 (t, *J* = 6.3 Hz, 2H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 200.5, 196.8, 140.0, 134.9, 129.7, 129.2, 37.8, 31.1; **FT-IR (thin film):** 1710, 1682, 1589, 1400, 1244, 1207, 1091, 983, 833 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{10}H_{10}ClO_2$ $[M+H]^+$ 197.0364; found: 197.0363.

4-(4-Bromophenyl)-4-oxobutanal (2h)



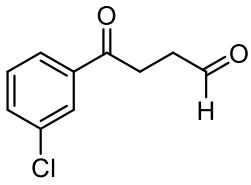
This compound was prepared according to the general procedure C. Reaction was completed after 3 h. Analytical TLC on silica gel using 12% ethyl acetate/hexane. White solid (44 mg, yield: 92%); **Mp:** 59-61 °C; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 9.90 (s, 1H), 7.85 (d, *J* = 8.4 Hz, 2H), 7.62 (d, *J* = 8.4 Hz, 2H), 3.29 (t, *J* = 6.0 Hz, 2H), 2.95 (t, *J* = 6.0 Hz, 2H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 200.6, 197.0, 135.3, 132.2, 129.8, 128.7, 37.7, 31.1; **FT-IR (thin film):** 1713, 1681, 1582, 1407, 1296, 1202, 1067, 998, 822, 715, 666 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{10}H_{10}BrO_2$ $[M+H]^+$ 240.9859; found: 240.9858.

4-(3-Methoxyphenyl)-4-oxobutanal (2i)



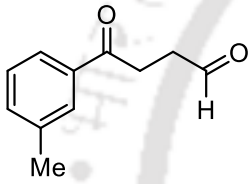
This compound was prepared according to the general procedure C. Reaction was completed after 4.5 h. Analytical TLC on silica gel using 18% ethyl acetate/hexane. Pale yellow oil (38 mg, yield: 98%); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.90 (s, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.50 (s, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.12 (dd, *J* = 2.8, 7.3 Hz, 1H), 3.85 (s, 3H), 3.13 (t, *J* = 6.6 Hz, 2H), 2.93 (t, *J* = 6.4 Hz, 2H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 200.8, 197.8, 160.0, 137.9, 129.8, 120,.9, 119.9, 112.5, 55.6, 37.8, 31.3; **FT-IR (thin film):** 1720, 1685, 1596, 1576, 1487, 1431, 1293, 1263, 1169, 1045, 788 cm^{-1}; **HRMS (+APCI):** Calcd for $C_{11}H_{13}O_3$ $[M+H]^+$ 193.0859; found: 193.0858.

4-(3-Chlorophenyl)-4-oxobutanal (2j)



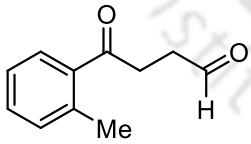
This compound was prepared according to the general procedure C. Reaction was completed after 3 h. Analytical TLC on silica gel using 12% ethyl acetate/hexane. Pale yellow oil (29 mg, yield: 74%); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 9.89 (s, 1H), 7.95 (s, 1H), 7.86 (d, *J* = 7.8 Hz, 1H), 7.54 (d, *J* = 9.0 Hz, 1H), 7.42 (t, *J* = 7.8 Hz, 1H), 3.29 (t, *J* = 6.3 Hz, 2H), 2.94 (t, *J* = 6.0 Hz, 2H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 200.4, 196.8, 138.2, 135.2, 133.4, 130.2, 128.4, 126.4, 37.7, 31.3; **FT-IR (thin film):** 1717, 1689, 1572, 1420, 1237, 1206, 1018, 997, 869, 789, 680 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{10}H_{10}ClO_2$ $[M+H]^+$ 197.0364; found: 197.0363.

4-Oxo-4-m-tolylbutanal (2k)



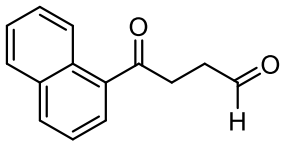
This compound was prepared according to the general procedure C. Reaction was completed after 4 h. Analytical TLC on silica gel using 15% ethyl acetate/hexane. Brown liquid (24 mg, yield: 68%); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 9.91 (s, 1H), 7.78 (d, *J* = 9.0 Hz, 2H), 7.34 – 7.40 (m, 2H), 3.32 (t, *J* = 6.6 Hz, 2H), 2.93 (t, *J* = 6.6 Hz, 2H), 2.41 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 200.9, 198.2, 138.7, 136.7, 134.3, 128.8, 128.7, 125.5, 37.9, 31.3, 21.6; **FT-IR (thin film):** 1722, 1685, 1603, 1587, 1362, 1255, 1161, 875, 785 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{11}H_{13}O_2$ $[M+H]^+$ 177.0910; found: 177.0900.

4-Oxo-4-o-tolylbutanal (2l)



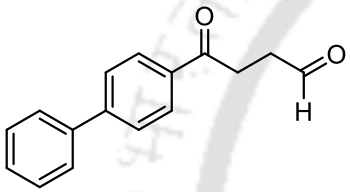
This compound was prepared according to the general procedure C. Reaction was completed after 3.5 h. Analytical TLC on silica gel using 15% ethyl acetate/hexane. Pale yellow oil (29 mg, yield: 82%); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 9.90 (s, 1H), 7.73 (d, *J* = 7.8 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.25 – 7.29 (m, 2H), 3.23 (t, *J* = 6.3 Hz, 2H), 2.91 (t, *J* = 6.3 Hz, 2H), 2.49 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 201.9, 200.8, 138.5, 137.5, 132.2, 131.7, 128.8, 125.9, 38.1, 33.9, 21.5; **FT-IR (thin film):** 1718, 1686, 1456, 1384, 1237, 1207, 1018, 977, 760 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{11}H_{13}O_2$ $[M+H]^+$ 177.0910; found: 177.0915.

4-(Naphthalen-5-yl)-4-oxobutanal (2m)



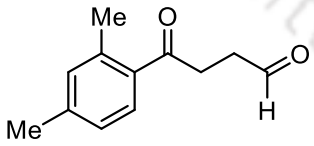
This compound was prepared according to the general procedure C. Reaction was completed after 2.5 h. Analytical TLC on silica gel using 15% ethyl acetate/hexane. Brown oil (32 mg, yield: 75%); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 9.95 (s, 1H), 8.58 (d, *J* = 8.4 Hz, 1H), 8.01 (d, *J* = 8.4 Hz, 1H), 7.97 (d, *J* = 6.6 Hz, 1H), 7.88 (d, *J* = 7.8Hz, 1H), 7.50 – 7.55 (m, 2H), 3.39 (t, *J* = 6.0 Hz, 2H), 3.02 (t, *J* = 6.3 Hz, 2H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 202.2, 200.9, 135.6, 134.1, 133.1, 130.3, 128.6, 128.2, 127.9, 126.7, 125.9, 124.6, 38.3, 34.5; **FT-IR (thin film):** 1717, 1677, 1595, 1509, 1394, 1235, 1178, 1104, 940, 805, 773 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{14}H_{13}O_2$ $[M+H]^+$ 213.0910; found: 213.0912.

4-(Biphenyl)-4-oxobutanal (2n)



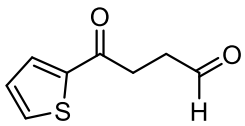
This compound was prepared according to the general procedure C. Reaction was completed after 5 h. Analytical TLC on silica gel using 15% ethyl acetate/hexane. Pale yellow solid (45 mg, yield: 95%); **Mp:** 93-95 ºC; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 9.93 (s, 1H), 8.06 (d, *J* = 8.4 Hz, 2H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 7.2 Hz, 2H), 7.48 (t, *J* = 7.8 Hz, 2H), 7.41 (t, *J* = 7.2 Hz, 1H), 3.37 (t, *J* = 6.3 Hz, 2H), 2.97 (t, *J* = 6.3 Hz, 2H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 200.9, 199.6, 146.2, 140.0, 135.3, 129.1, 128.9, 128.8, 127.6, 127.4, 37.8, 31.2; **FT-IR (thin film):** 1711, 1680, 1448, 1405, 1384, 1245, 1197, 981, 766, 724, 690 cm^{-1}; **HRMS (+APCI):** Calcd for $C_{16}H_{15}O_2$ $[M+H]^+$ 239.1067; found: 239.1068.

***4-(2,4-Dimethylphenyl)-4-oxobutanal* (*2o*)**



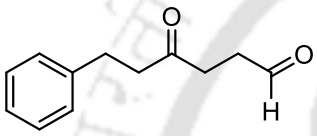
This compound was prepared according to the general procedure C. Reaction was completed after 4 h. Analytical TLC on silica gel using 15% ethyl acetate/hexane. Brown liquid (37 mg, yield: 97%); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 9.90 (s, 1H), 7.68 (d, *J* = 7.8 Hz, 1H), 7.07 (d, *J* = 11.4 Hz, 2H), 3.24 (t, *J* = 6.3 Hz, 2H), 2.89 (t, *J* = 6.0 Hz, 2H), 2.48 (s, 3H), 2.35 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 201.1, 200.9, 142.5, 139.2, 134.3, 133.2, 129.4, 126.6, 38.2, 33.6, 21.9, 21.6; **FT-IR (thin film):** 1720, 1680, 1611, 1566, 1448, 1234, 1206, 1140, 981, 814 cm^{-1}; **HRMS (+APCI):** Calcd for $C_{12}H_{15}O_2$ $[M+H]^+$ 191.1067; found: 191.1068.

4-Oxo-4-(thiophen-2-yl)butanal (2p)



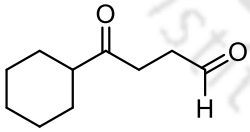
This compound was prepared according to the general procedure C. Reaction was completed after 2 h. Analytical TLC on silica gel using 15% ethyl acetate/hexane. Brown oil (30 mg, yield: 89%); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 9.88 (s, 1H), 7.77 (d, *J* = 4.2 Hz, 1H), 7.65 (d, *J* = 4.8 Hz, 1H), 7.14 (t, *J* = 4.2 Hz, 1H), 3.26 (t, *J* = 6.6 Hz, 2H), 2.93 (t, *J* = 6.6 Hz, 2H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 200.5, 190.9, 143.7, 134.0, 132.3, 128.4, 37.8, 31.7; **FT-IR (thin film):** 1723, 1662, 1518, 1416, 1246, 1054, 928, 854, 728 cm^{-1}; **HRMS (+ESI):** Calcd for $C_8H_9O_2S$ $[M+H]^+$ 169.0318; found: 169.0319.

4-Oxo-6-phenylhexanal (2q)



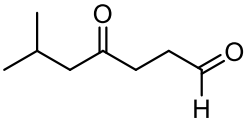
This compound was prepared according to the general procedure C. Reaction was completed after 10 h. Analytical TLC on silica gel using 12% ethyl acetate/hexane. Brown liquid (25 mg, yield: 65%); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.79 (s, 1H), 7.28 (t, *J* = 7.6 Hz, 2H), 7.19 (t, *J* = 8.0 Hz, 3H), 2.91 (t, *J* = 7.2 Hz, 2H), 2.80 (t, *J* = 7.2 Hz, 2H), 2.77 – 2.74 (m, 2H), 2.71 – 2.68 (m, 2H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 207.9, 200.6, 141.0, 128.7, 128.5, 126.3, 44.4, 37.6, 35.0, 29.9; **FT-IR (thin film):** 1712, 1599, 1435, 1409, 1263, 1100, 877, 751, 700 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{12}H_{15}O_2$ $[M+H]^+$ 191.1067; found: 191.1066.

4-Cyclohexyl-4-oxobutanal (2r)



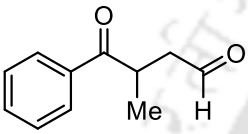
This compound was prepared according to the general procedure C. Reaction was completed after 20 h. Analytical TLC on silica gel using 15% ethyl acetate/hexane. Pale yellow oil (26 mg, yield: 77%); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 9.80 (s, 1H), 2.73 – 2.77 (m, 4H), 2.39 (t, *J* = 11.1 Hz, 1H), 1.88 (d, *J* = 11.4 Hz, 2H), 1.78 (d, *J* = 13.2 Hz, 2H), 1.23 – 1.37 (m, 5H), 1.20 (t, *J* = 12.6 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 212.1, 200.9, 50.9, 37.6, 32.8, 28.7, 26.0, 25.8; **FT-IR (thin film):** 1705, 1632, 1448, 1386, 1146, 1018 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{10}H_{17}O_2$ $[M+H]^+$ 169.1223; found: 169.1223.

6-Methyl-4-oxoheptanal (2s)



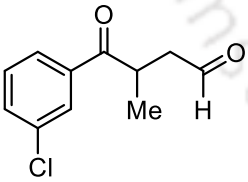
This compound was prepared according to the general procedure C. Reaction was completed after 24 h. Analytical TLC on silica gel using 15% ethyl acetate/hexane. Yellow oil (23 mg, yield: 81%); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 9.80 (s, 1H), 2.72 (d, *J* = 16.8 Hz, 4H), 2.33 (d, *J* = 6.0 Hz, 2H), 2.18 – 2.10 (m, 1H), 0.91 (d, *J* = 3.6 Hz, 6H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 208.7, 200.7, 51.9, 37.6, 35.4, 24.9, 22.7; **FT-IR (thin film):** 1712, 1468, 1386, 1368, 1170, 1140, 1080, 1033, 872 cm^{-1}; **HRMS (+APCI):** Calcd for $C_8H_{15}O_2$ $[M+H]^+$ 143.1067; found: 143.1068.

3-Methyl-4-oxo-4-phenylbutanal (2t)



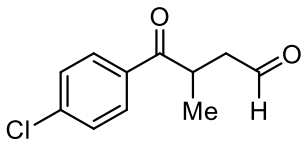
This compound was prepared according to the general procedure C. Reaction was completed after 48 h. Analytical TLC on silica gel using 15% ethyl acetate/hexane. Colorless oil (18 mg, yield: 51%); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 9.81 (s, 1H), 7.98 (d, *J* = 7.8 Hz, 1H), 7.58 (t, *J* = 7.2 Hz, 1H), 7.48 (t, *J* = 7.2 Hz, 2H), 4.03 – 3.97 (m, 1H), 3.17 (dd, *J* = 18.3, 7.8 Hz, 1H), 2.62 (dd, *J* = 18.6, 4.8 Hz, 1H), 1.24 (d, *J* = 7.2 Hz, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 202.7, 200.7, 135.8, 133.4, 128.9, 128.7, 47.3, 35.3, 18.2; **FT-IR (thin film):** 1711, 1681, 1596, 1449, 1380, 1240, 1179, 979, 794, 704 cm^{-1}; **HRMS (+APCI):** Calcd for $C_{11}H_{13}O_2$ $[M+H]^+$ 177.0910; found: 177.0909.

4-(3-Chlorophenyl)-3-methyl-4-oxobutanal (2u)



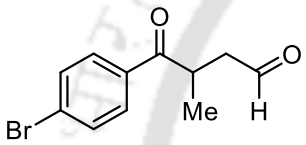
This compound was prepared according to the general procedure C. Reaction was completed after 30 h. Analytical TLC on silica gel using 15% ethyl acetate/hexane. Yellow oil (28 mg, yield: 67%); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 9.78 (s, 1H), 7.94 (s, 1H), 7.85 (d, *J* = 7.8 Hz, 1H), 7.55 (d, *J* = 7.8 Hz, 1H), 7.42 (d, *J* = 7.8 Hz, 1H), 3.95 – 3.89 (m, 1H), 3.19 (dd, *J* = 18.6, 8.4 Hz, 1H), 2.64 (dd, *J* =18.6, 4.8 Hz, 1H), 1.22 (d, *J* = 7.2 Hz, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 201.5, 200.4, 137.5, 135.3, 133.3, 130.3, 128.8, 126.7, 47.3, 35.4, 18.0; **FT-IR (thin film):** 1726, 1685, 1570, 1239, 1198, 1075, 801, 736, 670 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{11}H_{12}ClO_2$ $[M+H]^+$ 211.0520; found: 211.0522.

4-(4-Chlorophenyl)-3-methyl-4-oxobutanal (2v)



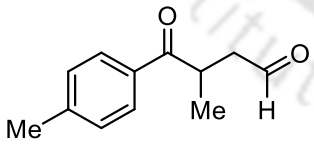
This compound was prepared according to the general procedure C. Reaction was completed after 30 h. Analytical TLC on silica gel using 15% ethyl acetate/hexane. Yellow oil (26 mg, yield: 62%); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.79 (s, 1H), 7.92 (d, *J* = 8.8 Hz, 2H), 7.45 (d, *J* = 8.8 Hz, 2H), 3.98 – 3.89 (m, 1H), 3.18 (dd, *J* = 18.8, 8.4 Hz, 1H), 2.62 (dd, *J* = 18.8, 4.8 Hz, 1H), 1.22 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 201.5, 200.5, 139.8, 134.2, 130.1, 129.3, 47.3, 35.2, 18.1; **FT-IR (thin film):** 1724, 1681, 1590, 1488, 1459, 1401, 1238, 1092, 1013, 980, 842, 748, 525 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{11}H_{12}ClO_2$ $[M+H]^+$ 211.0520; found: 211.0522.

4-(4-Bromophenyl)-3-methyl-4-oxobutanal (2w)



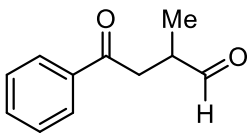
This compound was prepared according to the general procedure C. Reaction was completed after 48 h. Analytical TLC on silica gel using 15% ethyl acetate/hexane. Yellow oil (30 mg, yield: 59%); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 9.78 (s, 1H), 7.84 (d, *J* = 8.4 Hz, 2H), 7.62 (d, *J* = 8.4 Hz, 2H), 3.95 – 3.89 (m, 1H), 3.17 (dd, *J* = 18.6, 8.4 Hz, 1H), 2.63 (dd, *J* = 18.6, 4.8 Hz, 1H), 1.22 (d, *J* = 7.2 Hz, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 201.7, 200.5, 134.7, 132.3, 130.2, 128.6, 47.3, 35.2, 18.1; **FT-IR (thin film):** 1713, 1681, 1585, 1397, 1071, 1010, 978, 838 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{11}H_{12}BrO_2$ $[M+H]^+$ 255.0015; found: 255.0017.

3-Methyl-4-oxo-4-p-tolylbutanal (2x)



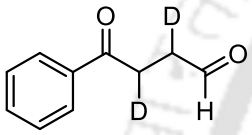
This compound was prepared according to the general procedure C. Reaction was completed after 72 h. Analytical TLC on silica gel using 15% ethyl acetate/hexane. Yellow oil (18 mg, yield: 47%); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 9.80 (s, 1H), 7.88 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), 3.99 – 3.96 (m, 1H), 3.14 (dd, *J* = 18.3, 8.1 Hz, 1H), 2.60 (dd, *J* = 18.6, 5.4 Hz, 1H), 2.42 (s, 3H), 1.23 (d, *J* = 8.4 Hz, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 202.3, 200.8, 144.2, 133.3, 129.6, 128.8, 47.3, 35.3, 21.9, 18.3; **FT-IR (thin film):** 1724, 1680, 1608, 1456, 1381, 1261, 1183, 1019, 801, 747 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{12}H_{15}O_2$ $[M+H]^+$ 191.1067; found: 191.1065.

2-Methyl-4-oxo-4-phenylbutanal (2y)



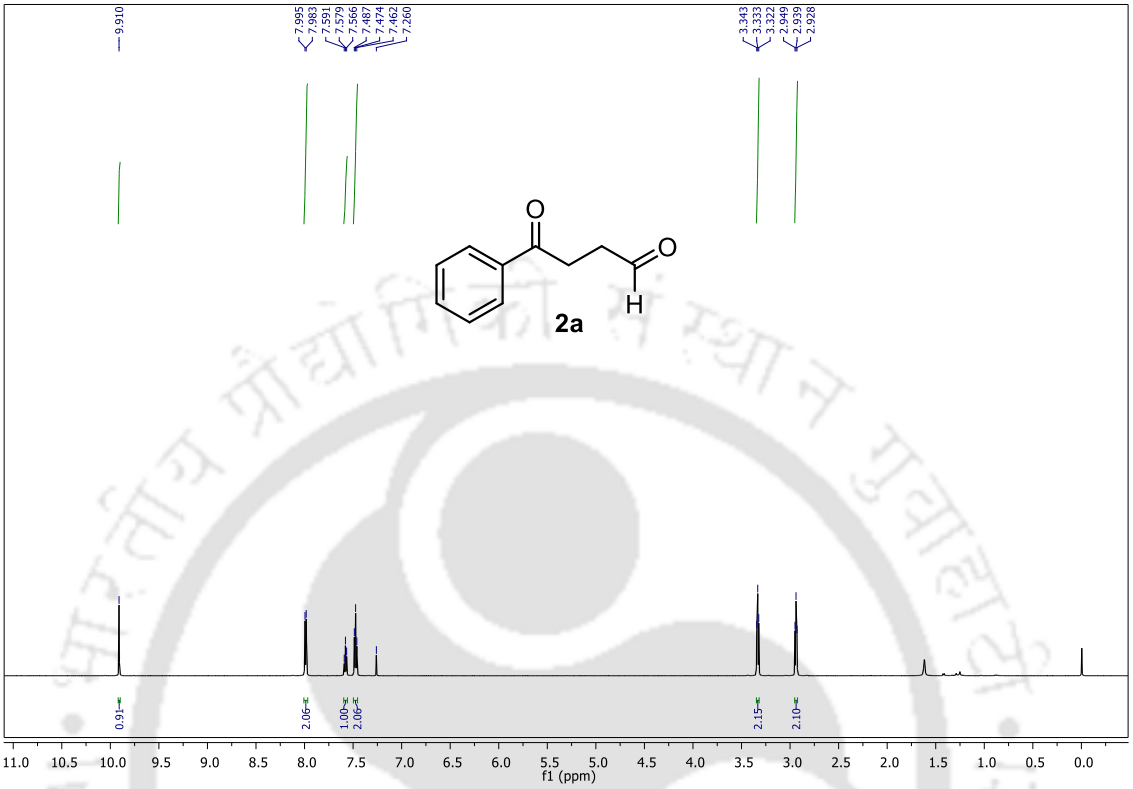
This compound was prepared according to the general procedure C. Reaction was completed after 30 h. Analytical TLC on silica gel using 15% ethyl acetate/hexane. Brown oil (17 mg, yield: 48%); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 9.80 (s, 1H), 7.98 (d, *J* = 7.8 Hz, 2H), 7.58 (t, *J* = 7.2 Hz, 1H), 7.48 (t, *J* = 8.4 Hz, 2H), 3.50 (dd, *J* = 18.0, 7.2 Hz, 1H), 3.16 – 3.10 (m, 1H), 3.26 (dd, *J* = 17.7, 6.0 Hz, 1H), 1.25 (d, *J* = 7.2 Hz, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 203.7, 198.0, 136.7, 133.6, 128.9, 128.3, 48.9, 39.6, 14.0; **FT-IR (thin film):** 1725, 1683, 1597, 1448, 1359, 1263, 1217, 1003, 913, 751, 690 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{11}H_{13}O_2$ $[M+H]^+$ 177.0910; found: 177.0912.

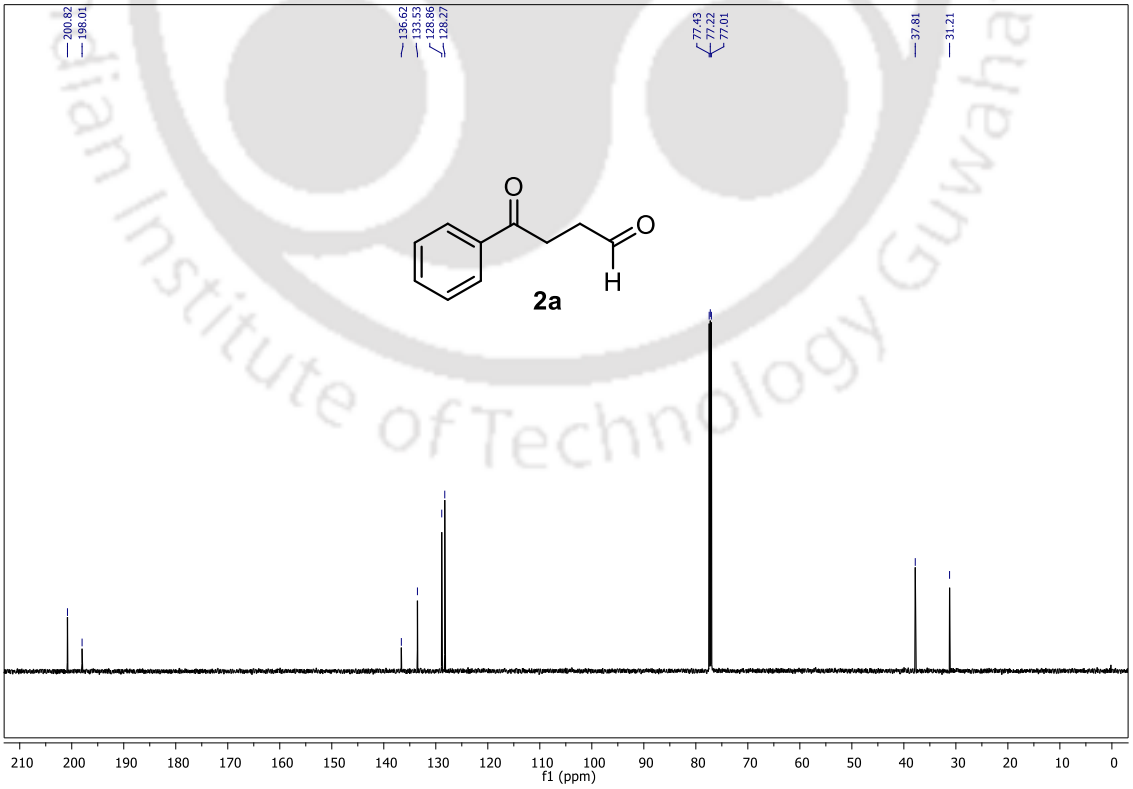
4-oxo-4-phenylbutanal-2,3-d_2

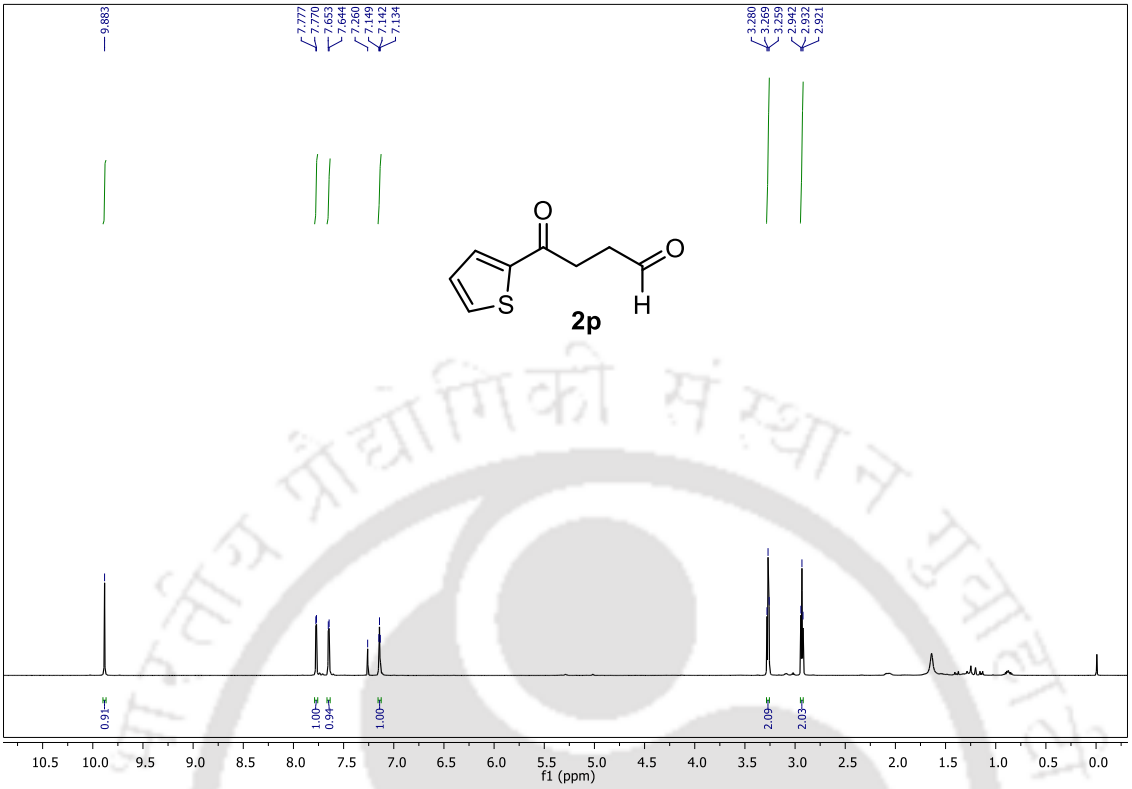


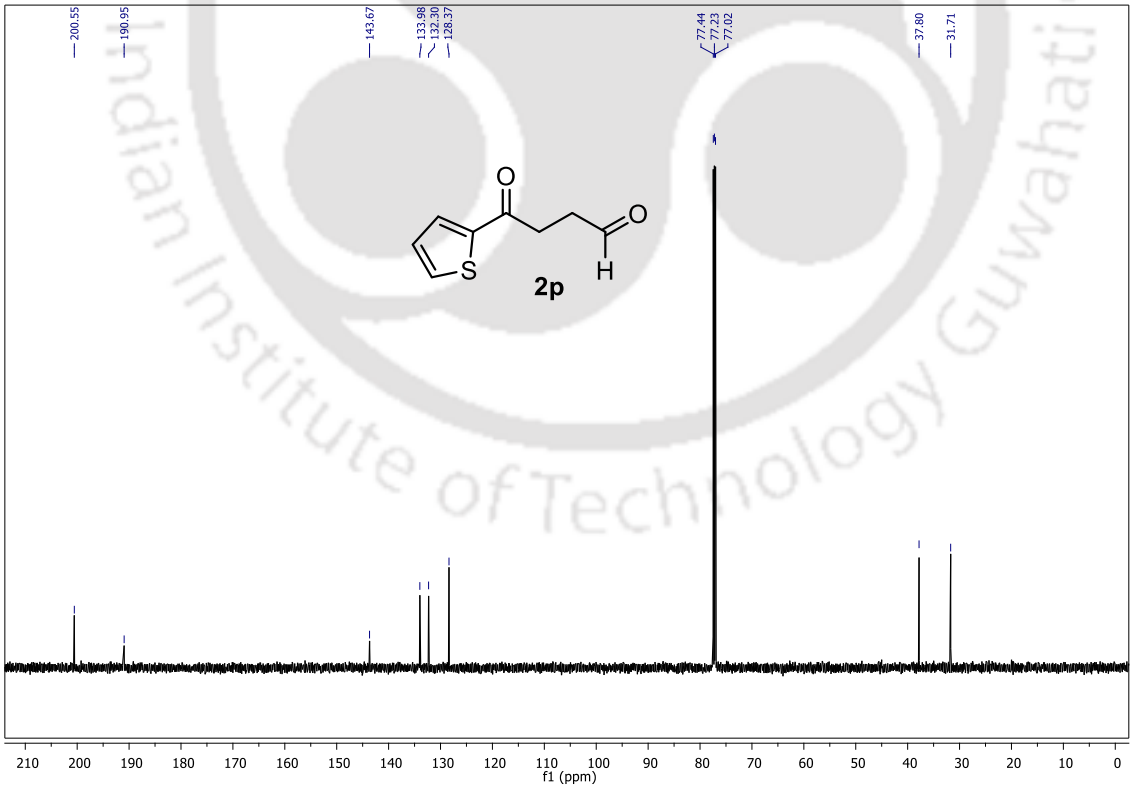
This compound was prepared according to the general procedure C in DMSO-*d6*/D_2O. Reaction was completed after 5 h. Analytical TLC on silica gel using 15% ethyl acetate/hexane. **^{1}H NMR (600 MHz, $CDCl_3$):** δ 9.91 (s, 1H), 7.99 (d, *J* = 7.8 Hz, 2H), 7.58 (t, *J* = 7.2 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 2H), 3.32 (t, *J* = 6.6 Hz, 1H), 2.92 (t, *J* = 6.6 Hz, 1H). **^{13}C NMR (150 MHz, $CDCl_3$):** δ 200.9, 198.0, 136.6, 133.5, 128.9, 128.3, 37.4 (t, *J* = 7.8 Hz), 30.9 (t, *J* = 7.8 Hz); **FT-IR (thin film):** 1724, 1682, 1597, 1448, 1280, 1220, 753, 690 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{10}H_{19}D_2O_2$ $[M+H]^+$ 166.0957; found: 166.0953.

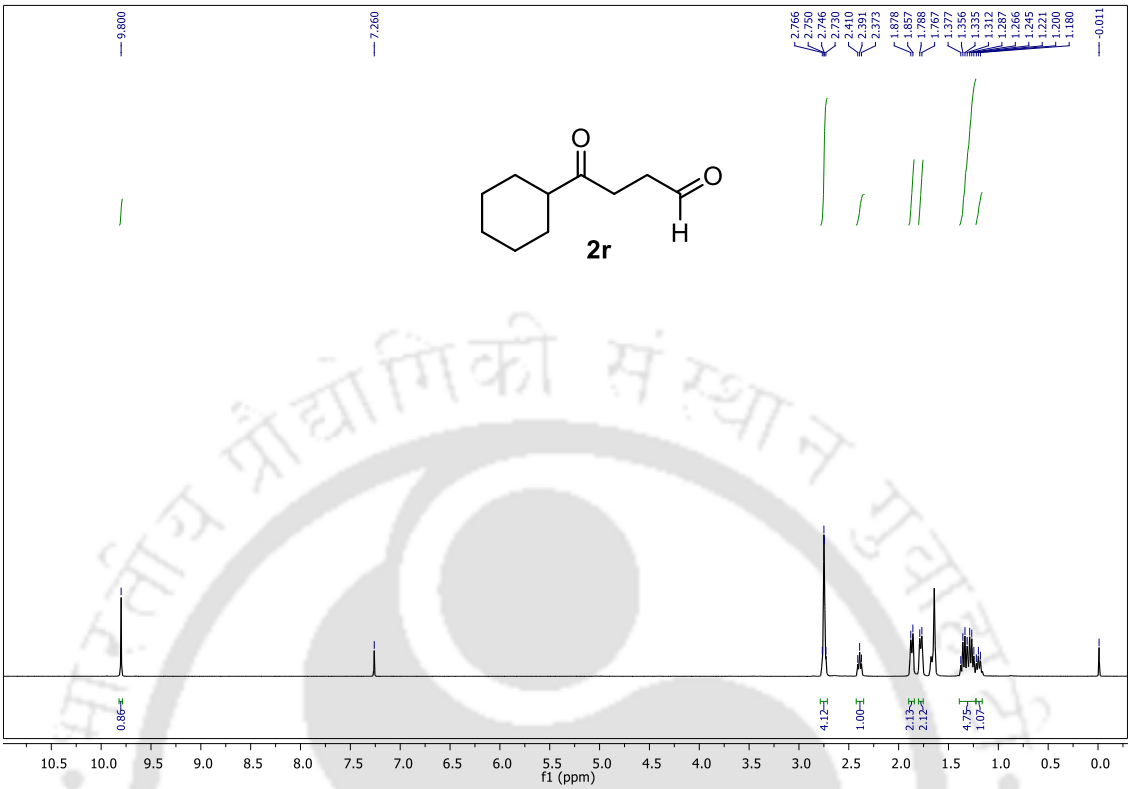
2.12 Selected NMR spectra of products

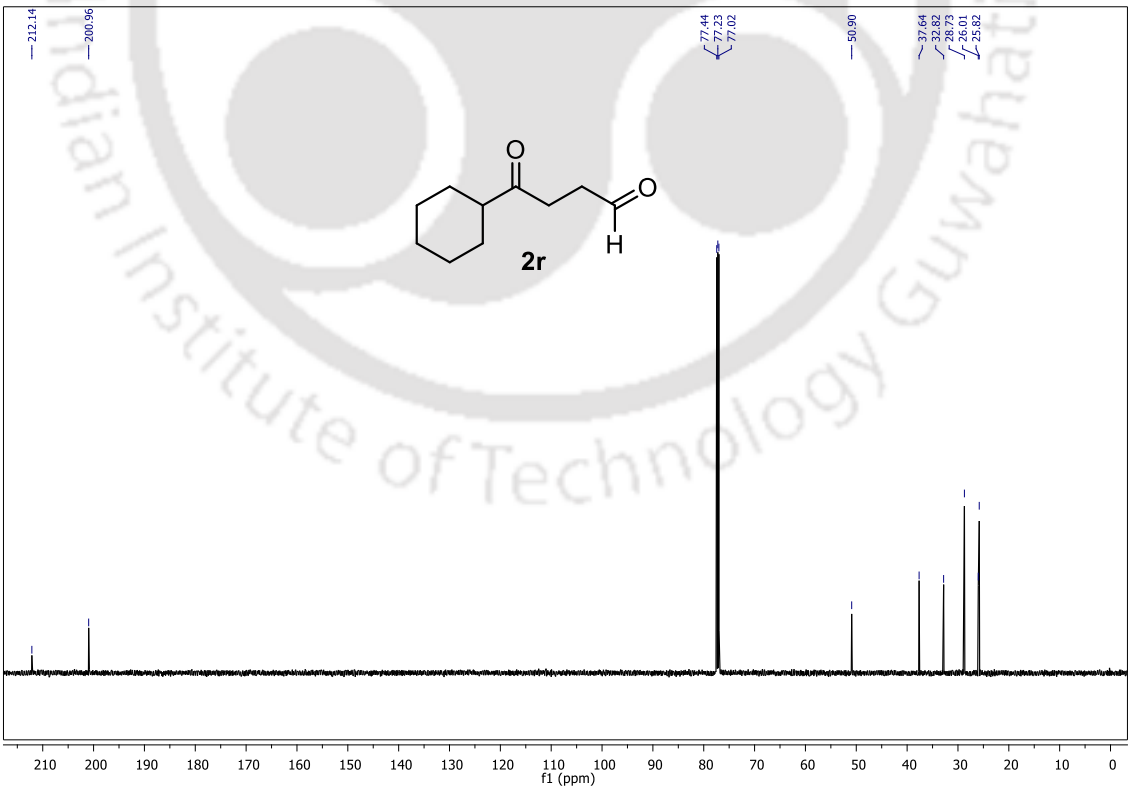


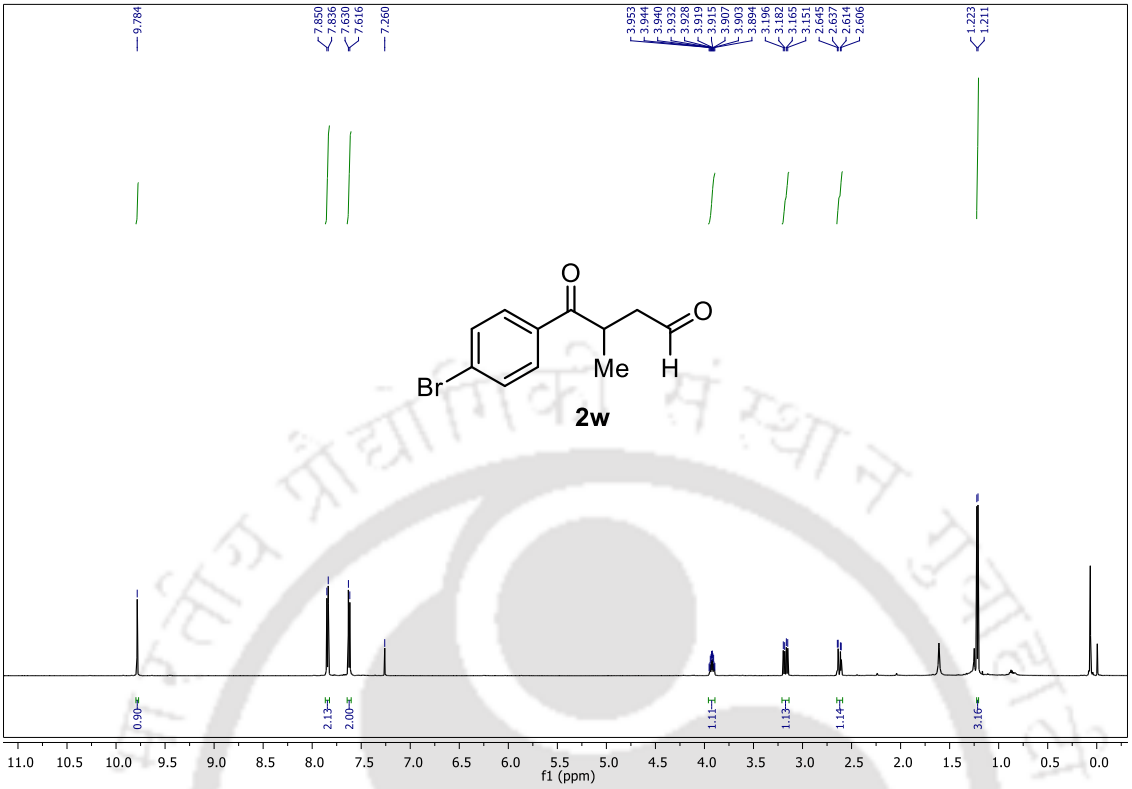


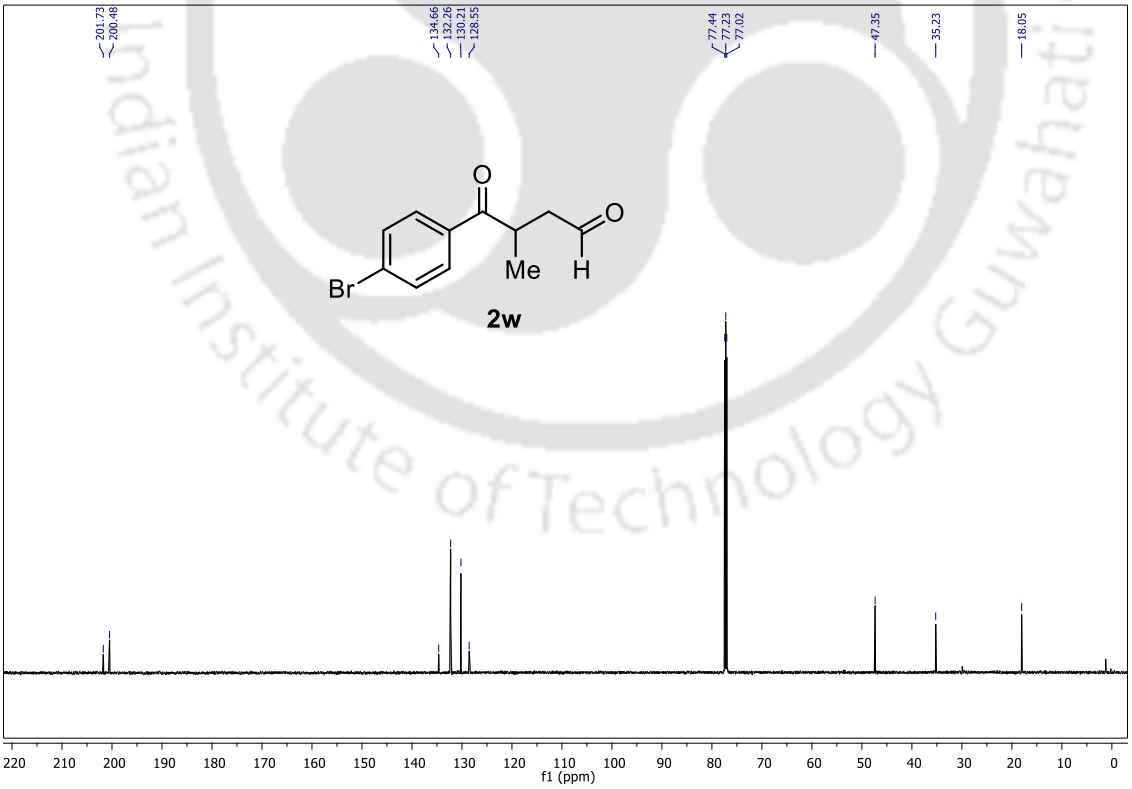












Chapter 3

Lewis Acid Catalyzed [3 + 3]-Annulation of Donor-Acceptor Cyclopropanes with γ-Hydroxyenones: Access to Highly Functionalized Tetrahydropyrans

3.1 Introduction

The tetrahydropyran ring is an important structural motif, present in wide range of natural products, such as antibiotics, pheromones and marine toxins, and some of the examples are depicted in Figure 3.1.[1] Also, the tetrahydropyran moiety is prevalent in many carbohydrates as well as in their oligomers and polymers that play vital roles in living organisms.[2]

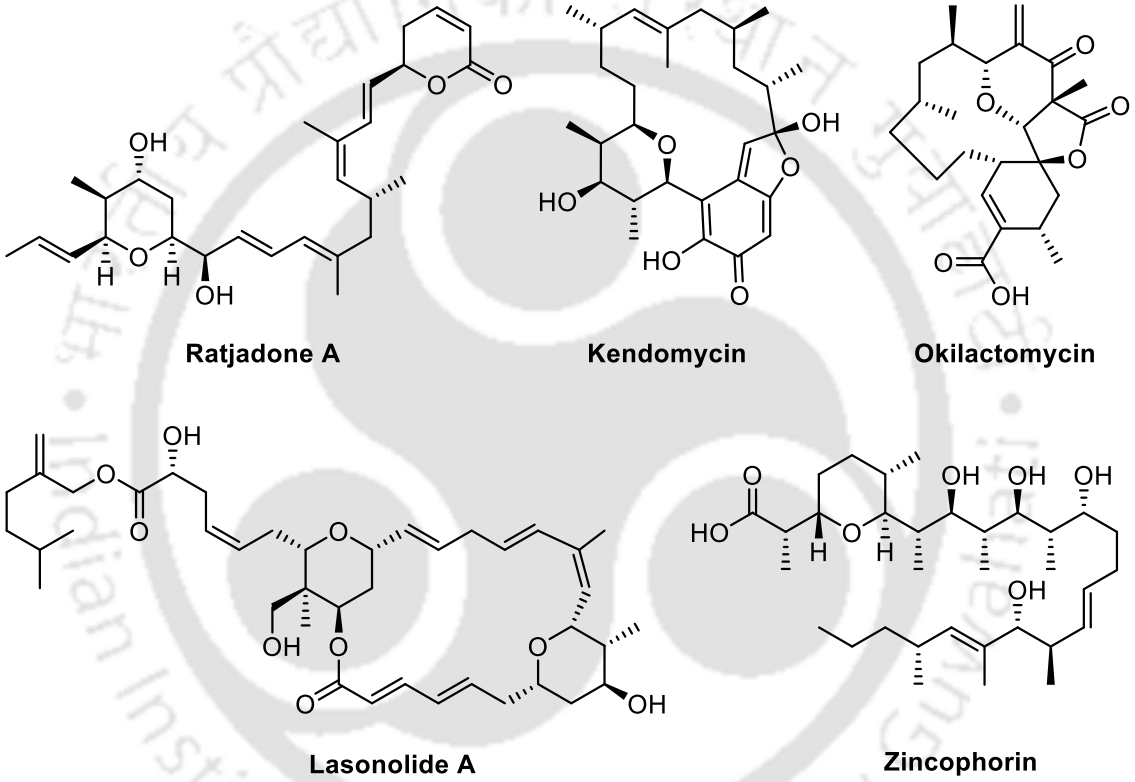


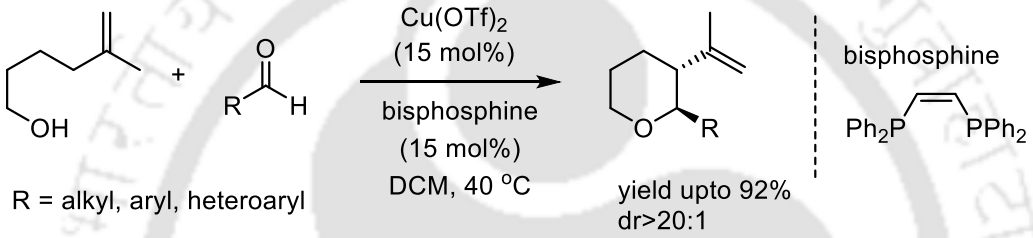
Figure 3.1: Biologically active natural products containing tetrahydropyran units

Owing to their impressive biological activities, the enormous emphasis has been put on the efficient construction of a variety of tetrahydropyrans.[3] These approaches included Prins cyclization,[4] the hetero-Diels-Alder cyclizations,[5] ring opening of epoxides,[6] radical cyclizations,[7] oxy-Michael additions[8] and many other methods. Though a large number of reactions based on the stereocontrolled and racemic approach have been developed for the construction of tetrahydropyrans but still there is a scope to synthesize tetrahydropyran ring with varied substitutions.

3.2 Known methods towards the synthesis of substituted tetrahydropyrans

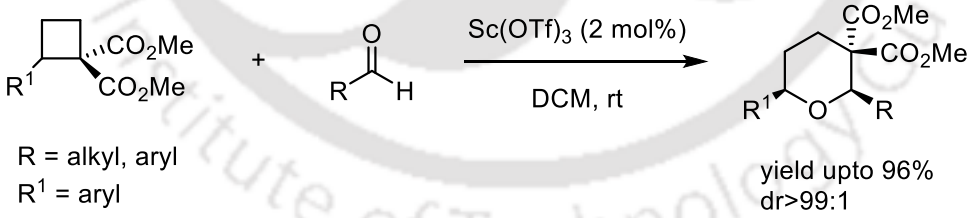
In the past decades, tetrahydropyrans have been used as an effective building block in organic synthesis, thus a large number of synthetic strategy has been developed for the preparation tetrahydropyran rings.[9] Some of the representative examples have been shown in this section.

Ghosh *et al*. accomplished the synthesis of highly diastereoselective substituted tetrahydropyran derivatives *via* sequential olefin migration and prins cyclization reaction between 5-olefin-1-ol and aldehyde in the presence of copper(II) triflate and bisphosphine ligand (Scheme 3.1).[10]



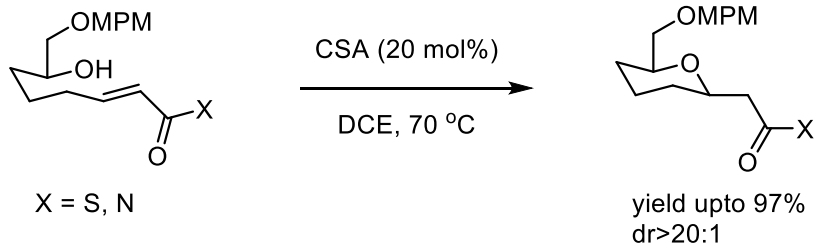
Scheme 3.1: Synthesis of tetrahydropyran using copper(II) triflate

Johnson group developed scandium(III) triflate catalyzed formal [4 + 2] cycloaddition reaction between donor-acceptor (DA) cyclobutanes and aldehydes to access highly diastereoselective tetrahydropyran derivatives (Scheme 3.2).[11]



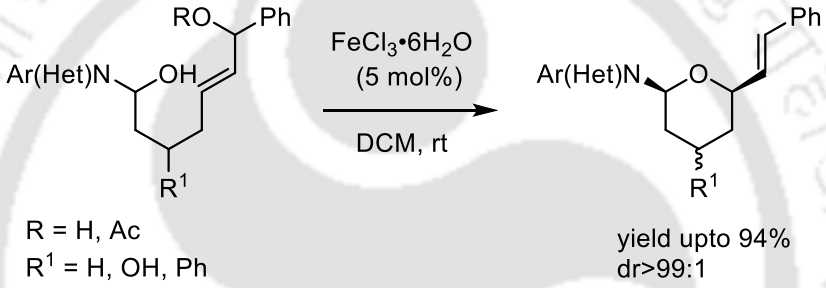
Scheme 3.2: Synthesis of tetrahydropyran *via* [4 + 2] cycloaddition reaction

Fuwa *et al*. described Brønsted acid catalyzed stereoselective formation of *cis*-substituted tetrahydropyrans *via* intramolecular oxy-Michael cyclization reaction of *α*,*β*-unsaturated ester system (Scheme 3.3).[12]



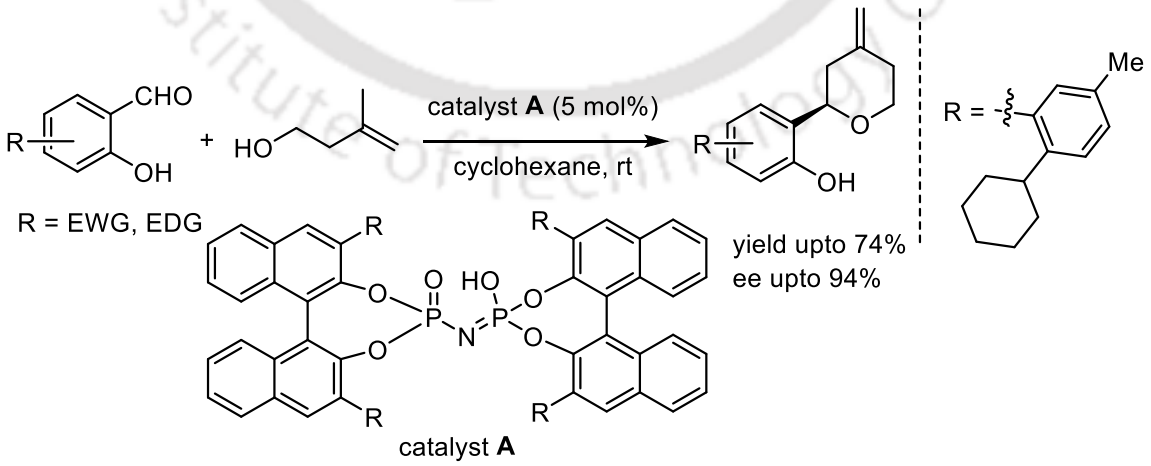
Scheme 3.3: Intramolecular oxy-Michael cyclization reaction

An iron catalyzed intramolecular cyclization reaction of hydroxyl allylic derivatives for the synthesis of tetrahydropyran compounds with high yields and *cis*-diastereoselectivity, was achieved by Cossy and co-workers (Scheme 3.4).[13]



Scheme 3.4: Iron(III)-catalyzed cyclization reaction for the synthesis of tetrahydropyran

Recently, iminophosphoric acid catalyzed asymmetric synthesis of tetrahydropyran *via* prins cyclization reaction was illustrated by List and co-workers, involving 2-hydroxy benzaldehyde and 4-en-1-ol and high enantioselectivity was observed (Scheme 3.5).[14]

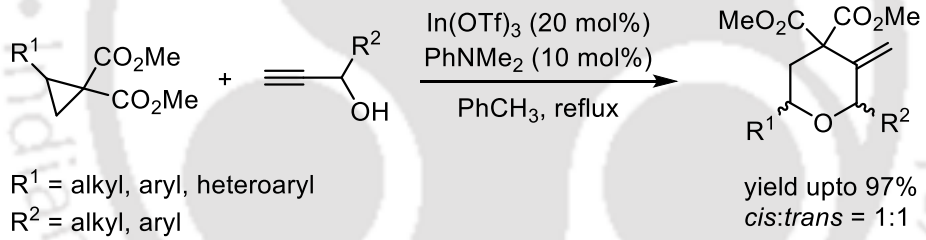


Scheme 3.5: Asymmetric synthesis of tetrahydropyrans

3.3 [3 + 3] annulation reactions using donor-acceptor cyclopropanes

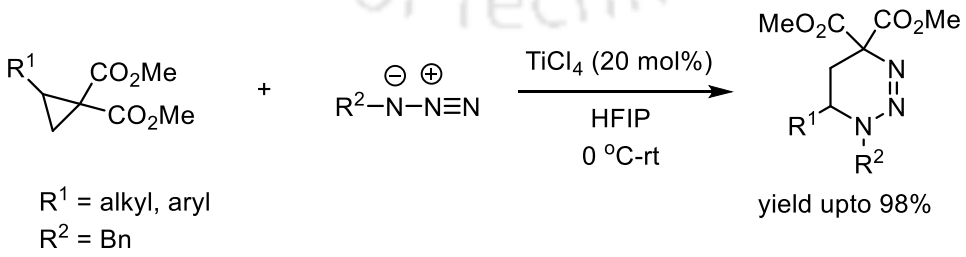
In the past few years, due to their unique reactivity profile donor-acceptor cyclopropanes (DA cyclopropanes) have served as an important synthetic intermediates in organic chemistry for the preparation of highly substituted carbo- and heterocycles *via* dipolar cycloaddition reaction, and thus directed towards the development of wide range of annulation reactions.[15] Among the [3 + *n*]-annulation reactions, the [3 + 3]-annulation reaction affords quick access to valuable six-membered rings.[16,17] For this purpose, a stable 1,3-zwitterion or substrate that could produce a dipolar species was required so that it could react with the reactive 1,3-dipole *in situ* generated from the DA cyclopropane in the presence of Lewis acid or base catalysts.

For example, Kerr and co-workers disclosed Lewis acid catalyzed nucleophilic ring opening of cyclopropane 1,1-diester by propargylic alcohol and subsequent conia-ene cyclization to afford substituted tetrahydropyrans with high yields and nearly 1:1 diastereomeric ratio (Scheme 3.6).[18]



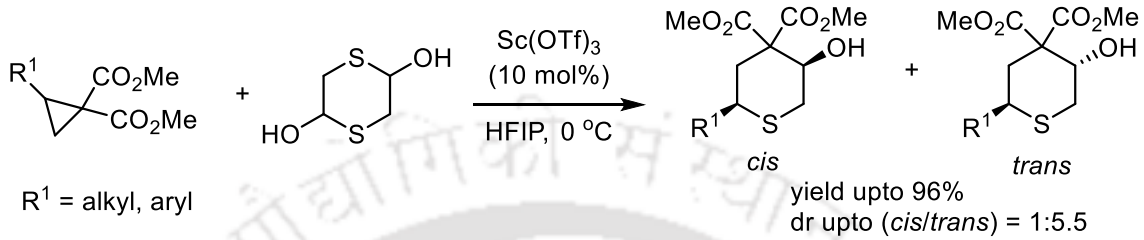
Scheme 3.6: Synthesis of tetrahydropyrans using DA cyclopropane

Afterward, in 2014, a $TiCl_4$ promoted formal [3 + 3] cycloaddition reaction of cyclopropane 1,1-diester and azides (used as a 1,3-dipole) was developed by Xu *et al*. for the synthesis of highly functionalized triazinines (Scheme 3.7).[19]



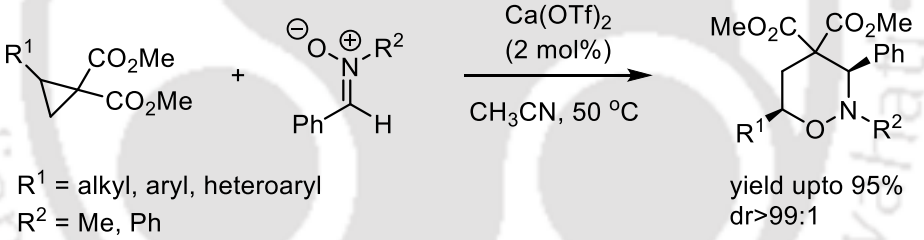
Scheme 3.7: Synthesis of triazinines using DA cyclopropane

Zhang group exploited [3 + 3] annulation reaction of cyclopropane 1,1-diester with *in situ* generated mercaptobenzaldehyde under the catalysis of scandium(III) triflate for the access to polysubstituted tetrahydrothiopyranols with moderate diastereoselectivities (Scheme 3.8).[20]



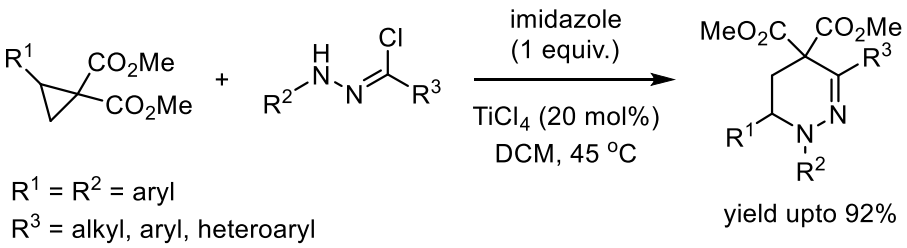
Scheme 3.8: Synthesis of tetrahydrothiopyranols using DA cyclopropane

Nolin and co-workers investigated that calcium(II) triflate has been proven to be an efficient catalyst for the cycloaddition reaction of 1,3 dipolar nitrone and donor-acceptor cyclopropane to produce the tetrahydro-1,2-oxazines with high level of diastereoselectivity (Scheme 3.9).[21]



Scheme 3.9: Synthesis of tetrahydro-1,2-oxazines using DA cyclopropane

Most recently, Werz group explored [3 + 3] cycloaddition of donor-accepter cyclopropane and nitrile imine (which was generated *in situ* from hydrazonyl chloride by imidazole) to afford the tetrahydropyridazines in the presence of titanium tetrachloride (Scheme 3.10).[22]



Scheme 3.10: Synthesis of tetrahydropyridazines using DA cyclopropane

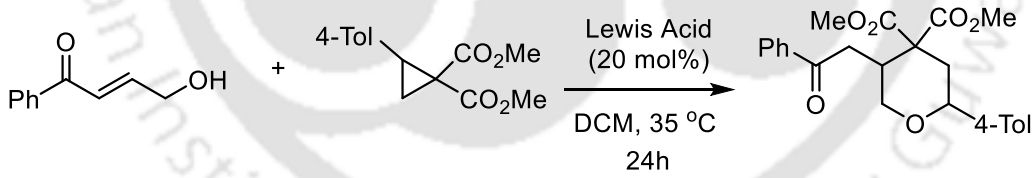
3.4 Result and discussion

Literature reports revealed that allylic alcohols have never been used in the reaction with donor-acceptor (DA) cyclopropanes till now and thus we envisioned that *γ*-hydroxyenones might be suitable 1,3-conjunctive reagents to undergo a tandem nucleophilic addition–Michael reaction. Encouraged by the prevalence of the tetrahydropyran unit in diverse natural products and in other compounds, we herein report a convenient Lewis acid catalyzed synthesis of 2,4,4,5-tetrasubstituted tetrahydropyran rings having two stereogenic centers, *via* reaction of *γ*-hydroxyenones with DA cyclopropanes.

The annulation reaction was initiated by performing a model reaction between 3-benzoylprop-2-en-1-ol (**1a**) and dimethyl 2-(4-methylphenyl) cyclopropane-1,1-dicarboxylate (**2a**) under the catalysis of $Yb(OTf)_3$ in DCM at 35 °C. The combined yield (50%) of [3 + 3]-annulation products **3a** (*cis*) and **3a′** (*trans*), which were obtained with 2:1 diastereomeric ratio (Table 1, entry 1). The relative structure of **3a** and **3a′** were determined by 2D NMR spectroscopy.

Optimization of reaction condition

Table 1: Catalyst screening



1a **2a** **3a**: *cis*, **3a'**: *trans*

entry[a]	catalyst (mol%)	yield (%)[b]	dr[c]
1	$Yb(OTf)_3$	50	2.1:1
2	$Cu(OTf)_2$	15	nd[d]
3	$SnCl_4$	25	nd
4	$Zn(OTf)_2$	trace	nd
5	$BF_3.Et_2O$	trace	nd

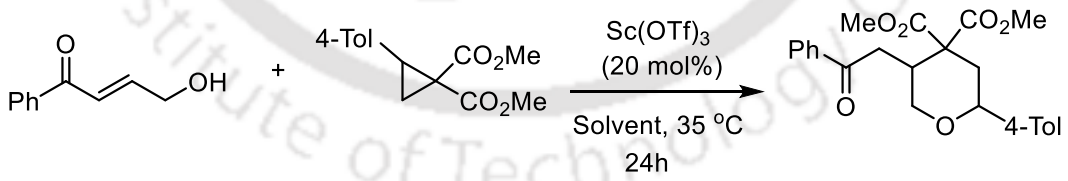
6	$MgBr_2$	trace	nd
7	$Sn(OTf)_2$	trace	nd
8	$TiCl_4$	trace	nd
9	$SnCl_2$	trace	nd
10	$Sc(OTf)_3$	85%	2:1

[a]Reaction conditions: Unless otherwise mentioned 0.1 mmol of **1a** and 0.2 mmol of **2a** in 0.5 mL DCM using 20 mol% catalyst at 35 °C for 24h. [b]Isolated yield after silica gel column chromatography. [c]Determined by ^{1}H NMR. [d]nd = not determined.

Deprived results were obtained with $Cu(OTf)_2$ and $SnCl_4$ respectively (Table 1, entries 2-3). However, only a trace amount of the [3 + 3]-annulation product was observed with Lewis acids such as $Zn(OTf)_2$, $BF_3{\cdot}OEt_2$, $MgBr_2$, $Sn(OTf)_2$, $TiCl_4$ and $SnCl_2$ (Table 1, entries 4-9). Gratifyingly, the yield was enhanced to 85% with $Sc(OTf)_3$ and an identical diastereomeric ratio of 2: 1 was observed (Table 1, entry 10).

Then, the same experiment was studied with different solvents and the results of which are illustrated in Table 2. Though other halogenated solvents such as DCE afforded decent yield (80%) of the products (Table 2, entry 2) but moderate yield (54%) was obtained with $CHCl_3$ (Table 2, entry 3).

Table 2. Solvent Screening



1a **2a** **3a**: *cis*, **3a'**: *trans*

entry[a]	solvent	yield (%)[b]	dr[c]
1	DCM	85	2.:1
2	DCE	80	1.8:1
3	$CHCl_3$	54	2:1

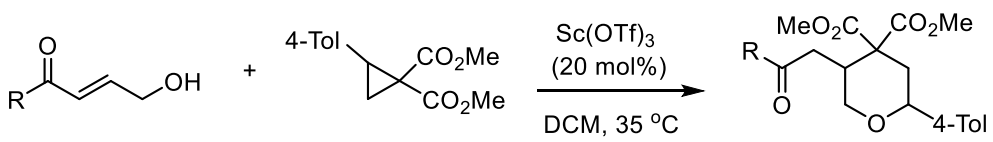
4	$PhCH_3$	74	1.7:1
5	CH_3CN	71	2.1:1
6	THF	73	2:1
7	DMF	trace	nd[d]
8	MeOH	trace	nd
9	1,4-Dioxane	trace	nd
10[e]	DCM	75	2:1
11[f]	DCM	45	2:1
12[g]	DCM	80	2:1

[a]Reaction conditions: Unless otherwise mentioned 0.1 mmol of **1a** and 0.2 mmol of **2a** in 0.5 mL solvent using 20 mol% catalyst at 35 °C for 24h. [b]Isolated yield after silica gel column chromatography. [c]Determined by ^{1}H NMR. [d]nd = not determined. [e]With 10 mol% catalyst. [f]With 5 mol% catalyst. [g]Using 1.5 equiv. of **2a**.

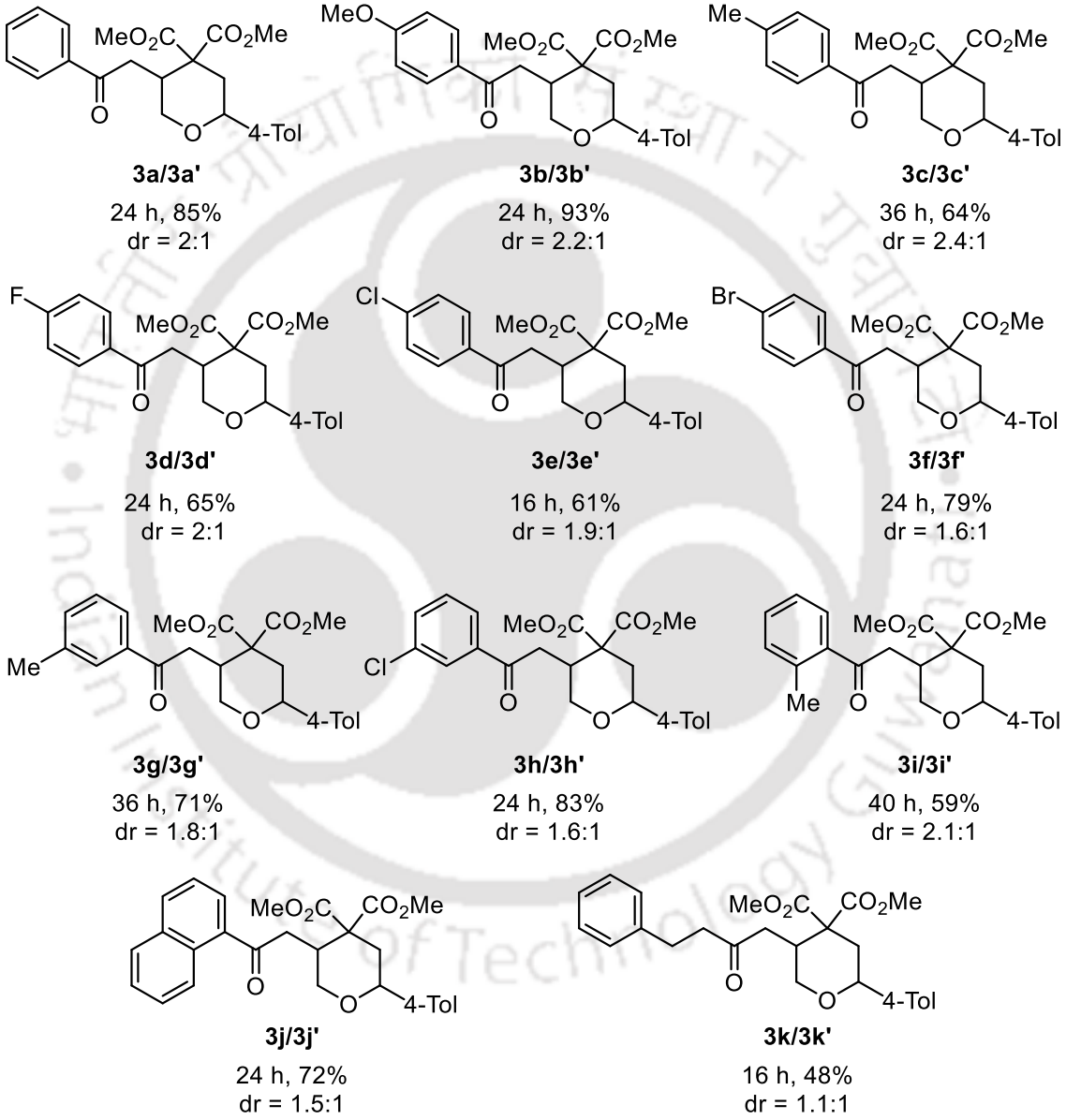
Also, good yields of 74%, 71% and 73% were observed with $PhCH_3$, CH_3CN, and THF respectively (Table 2, entries 4-6). Other solvents such as DMF, MeOH, and 1,4-dioxane provided only trace amounts of the desired products (Table 2, entries 7-9). Then, we focused on decreasing the catalyst loading amount of $Sc(OTf)_3$ from 20 mol% to 10 and 5 mol% in DCM but lower yields of the product were observed (Table 2, entries 10-11). When the reaction was performed using 1.5 equiv. of **2a**, under the same reaction condition, the yield of the reaction slightly decreased (Table 2, entry 12).

3.5 Substrate scope

After identifying the optimized conditions, the scope of the reaction was studied. Initially, a variety of *γ*-hydroxyenones **1** were examined with cyclopropane-1,1-diester **2a** (Scheme 3.11). Pleasingly, different electron-withdrawing and electron-donating groups could be embedded in the *ortho*, *meta*, and *para* positions of the aryl group. An excellent yield of 93% was achieved for the diastereomeric products **3b**/**3b′** having *p*-anisyl group. Enone **1c**, having *p*-tolyl motif, provided the corresponding products **3c**/**3c′** in relatively less yields (64%) with 2.4:1 diastereomeric ratio.



1a-1k **2a** **3a-3k**: *cis*, **3a'-3k'**: *trans*



3a/3a'
24 h, 85%
dr = 2:1

3b/3b'
24 h, 93%
dr = 2.2:1

3c/3c'
36 h, 64%
dr = 2.4:1

3d/3d'
24 h, 65%
dr = 2:1

3e/3e'
16 h, 61%
dr = 1.9:1

3f/3f'
24 h, 79%
dr = 1.6:1

3g/3g'
36 h, 71%
dr = 1.8:1

3h/3h'
24 h, 83%
dr = 1.6:1

3i/3i'
40 h, 59%
dr = 2.1:1

3j/3j'
24 h, 72%
dr = 1.5:1

3k/3k'
16 h, 48%
dr = 1.1:1

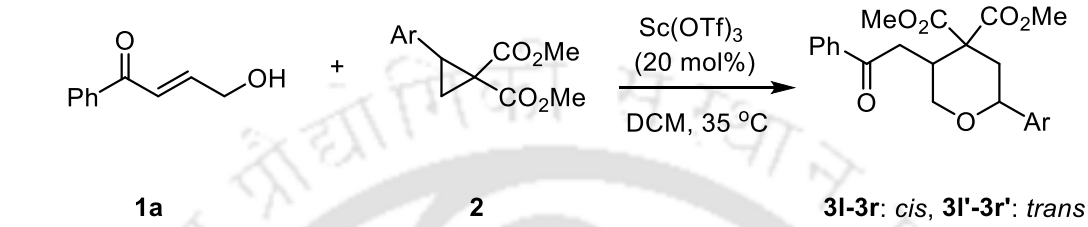
[a]Reaction conditions: All reactions were carried out with 20 mol% of $Sc(OTf)_3$ in DCM at 35 °C. [b]Combined yield for isolated product after silica gel column chromatography. [c]Determined by ^1H NMR.

Scheme 3.11: Scope of tetrahydropyran with different γ-hydroxyenones[a,b,c]

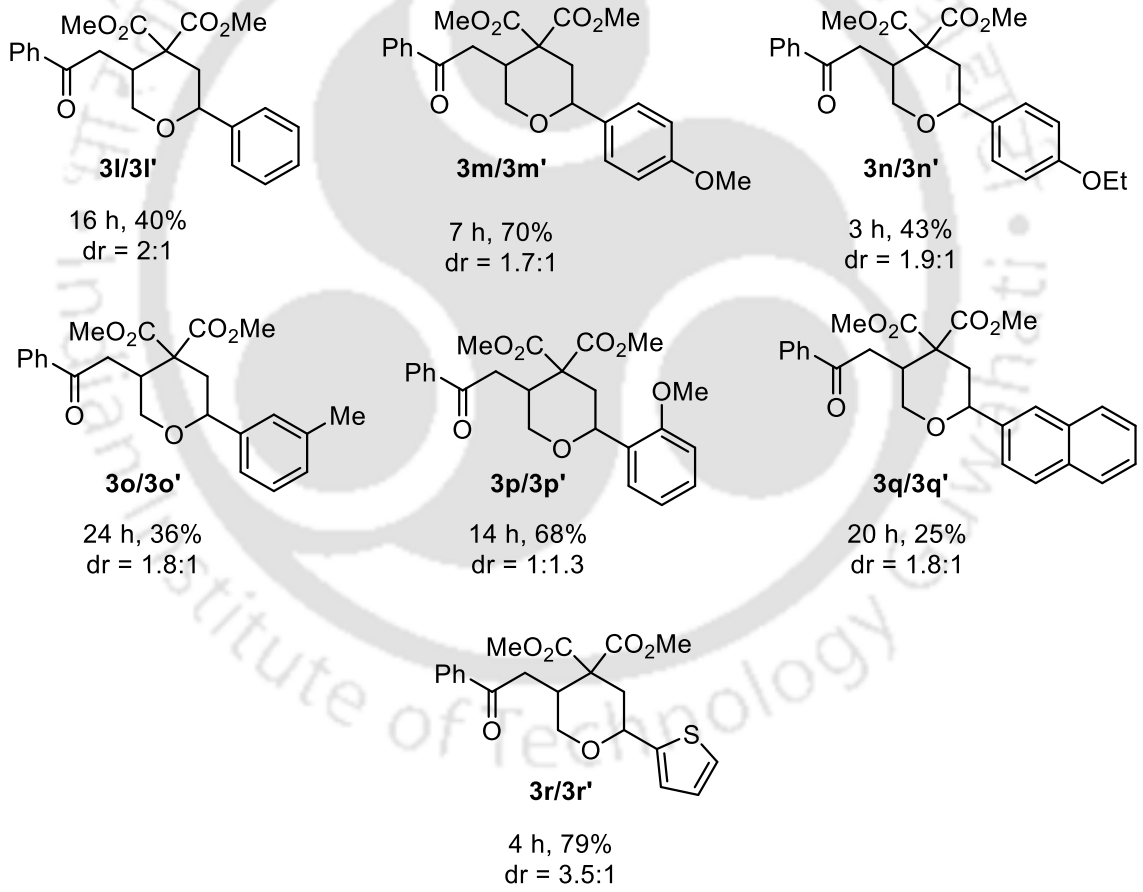
Enones, containing 4-halo-substituted aryl groups, were also screened and the products were attained with acceptable yields. The corresponding products **3d/3d′** and **3e/3e′**, having 4-fluoro and 4-chloro substituents, were isolated with comparable yields and diasteroselectivities. Interestingly, better yield (79%) was obtained for the compounds **3f/3f′** with a little lower diastereomeric ratio. Next, different substituents in the *meta* position were explored and it did not significantly affect the reaction and high yields were maintained. For example, 3-methyl and 3-chloro substituted enones provided the analogous products **3g/3g′** (71%) and **3h/3h′** (83%) with similar diastereocontrol. *Ortho*-substitution of the aryl group was also tolerated and the products **3i/3i′** were obtained with 59% combined yield. The reaction also progressed well for enone **1j** containing a 1-naphthyl group under our reaction conditions, delivering the products **3j/3j′** with 72% yield and slightly lower diastereomeric ratio. To our delight, this methodology was also suitable for an aliphatic enone. For example, hydrocinnamyl-substituted enone **1k** gave products **3k/3k′**, with low yield and 1:1 diastereoselectivity. Unfortunately, other aliphatic substituted enones (e.g. cyclohexyl, *tert*-butyl, etc.) did not deliver the desired products under the same reaction conditions.

Next, we sought to enhance the generality of the reaction by incorporating a range of cyclopropane-1,1-diesters (Scheme 3.12). Though a variety of substituents on the aryl group was tolerated, only trace amounts of the products were obtained with electron-poor aryl groups, possibly due to the instability of the resulting positive charge that is generated during ring opening of cyclopropane-1,1-diesters. Thus, we thought to synthesize a range of cyclopropane-1,1-diesters bearing electron-rich aryl and hetero-aromatic groups. Phenyl-containing cyclopropane-1,1-diester **2b** delivered the products **3l/3l′** with 40% yield but pleasingly, a higher yield of 70% was achieved within a short time frame for products **3m/3m′** having a *p*-anisyl substituent. A moderate yield (43%) was attained after 3 h with **2d** having a *p*-ethoxyphenyl substituent while running the reaction for a longer time resulted in the formation of undesired side products. Similarly, *m*-tolylsubstituted diester **2e** underwent the reaction to deliver products **3o/3o′**, with low yield, owing to the side-product formation. Though the outcome was better with *o*-anisyl substituted diester **2f** providing the products **3p/3p′** with 68% yield and 1:1.3

diastereomeric ratio. Gratifyingly, 2-naphthyl-substituted diester **2g** could also be employed in our reaction, although a lower yield was observed. Finally, heteroaromatic substrate like thiophene-containing diester **2h** was engaged in the reaction, and a decent yield of 79% was attained with a high diastereomeric ratio 3.5:1 within a short reaction time (Scheme 3.12).



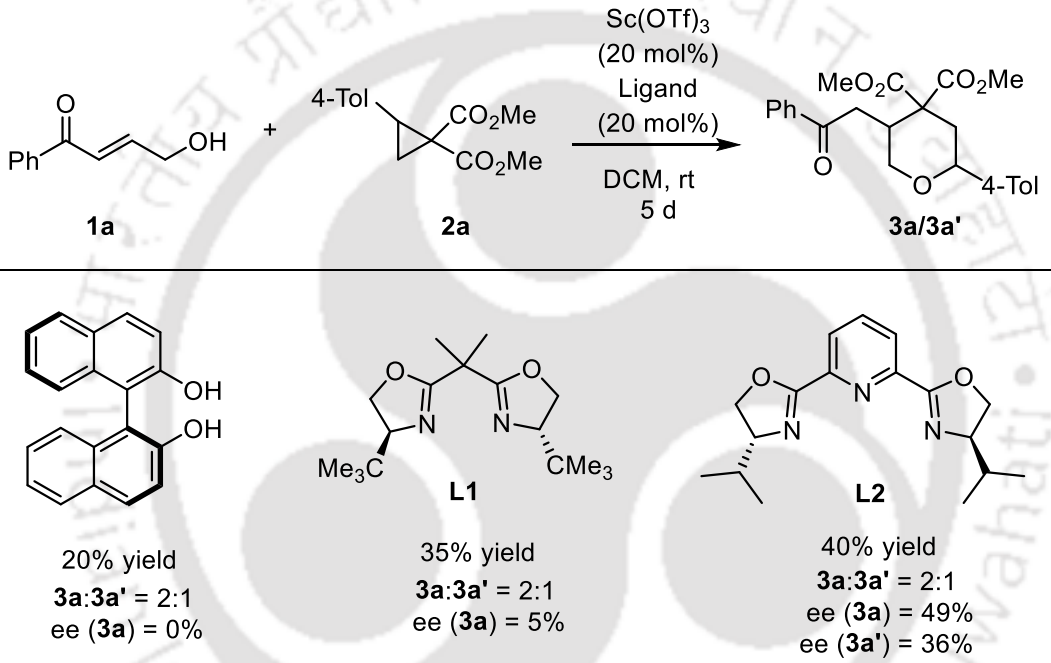
1a **2** **3l-3r**: *cis*, **3l'-3r'**: *trans*



[a]Reaction conditions: All reactions were carried out with 20 mol% of $Sc(OTf)_3$ in DCM at 35 °C. [b]Combined yield for isolated product after silica gel column chromatography. [c]Determined by ^1H NMR.

Scheme 3.12: Scope of tetrahydropyran with different cyclopropane-1,1-diesters[a,b,c]

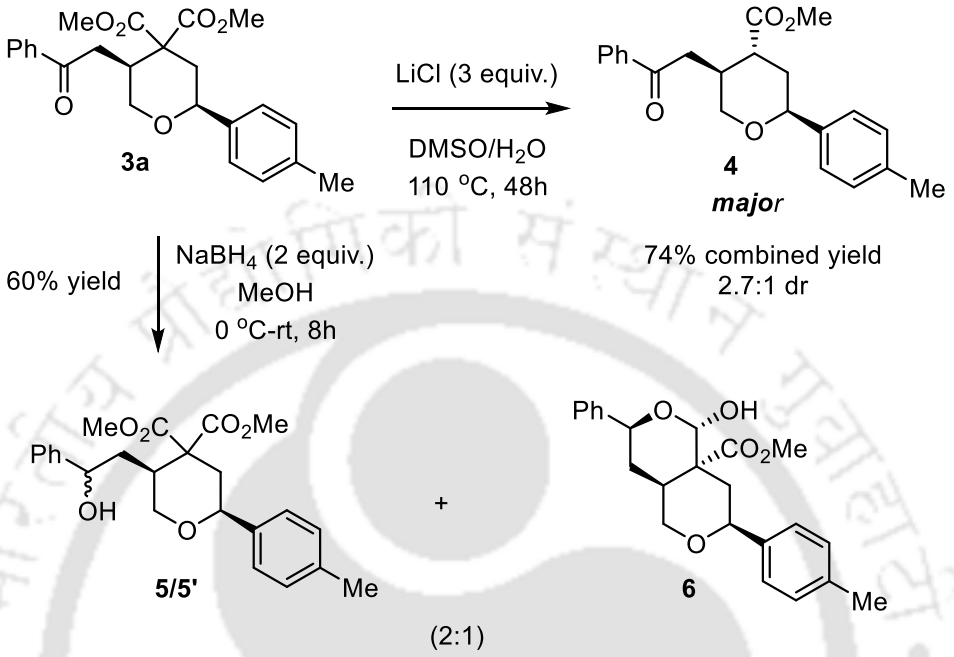
Afterward, the possibility of the asymmetric version of this reaction was studied (Scheme 3.13).[23] Accordingly, **1a** was treated with cyclopropane diester **2a** in the presence of catalytic amounts of different chiral ligands and $Sc(OTf)_3$. 1,1′-Bi-2 naphthol (BINOL) and *tert*-leucine-derived BOX catalyst **L1** provided the products **3a/3a′** with very poor enantioselectivities (<5 % *ee*). However, gratifyingly, a promising result was obtained by using PyBOX catalyst **L2**. With **L2** (20 mol%) and $Sc(OTf)_3$ (20 mol%), the major diastereomer was achieved with 49% *ee* (minor 36% *ee*) in 40% overall yield (Scheme 3.13).



Scheme 3.13: Asymmetric version of the reaction

Further, to demonstrate the synthetic utility of our method, a few reactions on our products were performed (Scheme 3.14). Purified *cis*-**3a** was thus treated with LiCl in $DMSO/H_2O$ at 110 °C.[24] To our delight, desired 2,4,5-trisubstituted tetrahydropyran products **4/4′** were isolated with 74% yield and 2.7:1 diastereomeric ratio. The structure of the major diastereomer **4** was determined by 2D NMR spectroscopy. Similarly, sodium borohydride reduction was performed on **3a** in methanol at 0 °C. Interestingly, besides normal alcohol products **5/5′**, lactol **6** was also formed with a 2:1 ratio. The structure of lactol **6** was unambiguously confirmed by X-ray crystallography.[25]

Presumably, lactol **6** was formed from lactone, and thus, it is an unusual reduction by sodium borohydride, as sodium borohydride generally does not reduce lactones.



Scheme 3.14: Synthetic transformations of the products

In summary, an interesting [3 + 3]-annulation reaction between γ-hydroxyenones and cyclopropane-1,1-diesters catalyzed by commercially available $Sc(OTf)_3$ has been developed. A preliminary experiment for a catalytic asymmetric variant was performed with a PyBOX ligand and 49% *ee* was achieved for the major *cis*-diastereomer. The tetrahydropyran products, having two stereogenic centers, are significant in the synthesis of pharmaceuticals and natural products.

3.6 Experimental section

General information

All reactions were carried out in oven dried glassware under argon atmosphere with magnetic stirring. Chemicals and solvents were purchased from commercial suppliers and used as received. Dichloromethane was distilled over CaH_2 under argon and stored over 4Å molecular sieves. All other solvents and reagents were purified according to standard procedures. Organic solvents were dried over anhydrous Na_2SO_4 and concentrated in a rotary evaporator under reduced pressure. For column chromatography, silica gel (60−120 mesh size) was used. For TLC analyses, precoated silica gel plates were used. ^{1}H NMR spectra were recorded using 400 MHz and 600 MHz spectrometers. ^{13}C NMR spectra were recorded using 100 MHz and 150 MHz spectrometers. Chemical shifts were reported in parts per million (ppm) and the residual solvent peak was used as an internal reference: proton (chloroform δ 7.26), carbon (chloroform δ 77.23). Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), brs (broad singlet). Coupling constants were reported in Hertz (Hz). IR spectra were recorded using an FT-IR Instrument at normal temperature by making KBr pellet and grinding the sample with KBr (IR grade). Mass spectra were recorded using a Q-TOF mass spectrometer.

Single crystal X-ray data were collected using Bruker SMART APEXII CCD diffractometer, which is equipped with 1.75 kW sealed-tube Mo-Kα irradiation (λ = 0.71073 Å) at 298(2) K and the structure was solved by direct methods using SHELXS-2014 (Göttingen, Germany) and refined with full-matrix least-squares on F^2 using SHELXL-2014.

A. General procedure for the synthesis of *trans*-γ- hydroxyenones 1a-1k

Trans-γ-hydroxyenones were prepared according to the reported procedure.[26]

B. General procedure for the synthesis of DA-cyclopropanes 2a-2h

All DA-cyclopropanes were synthesized using literature reported procedure.[27]

C. General procedure for the synthesis of annulation products 3a/3a′-3r/3r′

Under argon atmosphere, compound **1** (0.1 mmol), cyclopropyl diester **2** (0.2 mmol) and catalyst $Sc(OTf)_3$ (20 mol%) were placed in a 10 mL Round Bottom Flask and 0.5 mL DCM solvent was added to it. Then the reaction mixture was stirred at 35 °C. After the reaction was completed as monitored by TLC, the reaction mixture was directly subjected to column chromatography on silica gel using 10% EtOAc/Hexane as an eluent to obtain the desired product **(3)**.

D. Representative procedure for asymmetric synthesis

In a flame-dried two-necked round-bottomed flask, $Sc(OTf)_3$ (20 mol%) and PyBox ligand **L2** (20 mol%) were placed in 0.25 mL DCM and stirred for 1 hour at room temperature. Then a solution of cyclopropane diester **2a** (0.2 mmol) and compound **1a** in 0.25 mL DCM was added to this reaction mixture and further stirred for 5 days at 35 °C. The crude reaction mixture was purified by flash chromatography on silica gel (15% EA/hexane) to give the desired product with 40% yield. The ee (49% ee_{major}, 36% ee_{minor}) were determined by HPLC using Chiralpak IB column with hexane/^{i}PrOH (95:5) as the eluent; flow: 1.0 mL/min; 254 nm; major diastereoisomer, t_{major} = 8.99 min, t_{minor} = 10.48 min; minor diastereoisomer, t_{major} = 9.76 min, t_{minor} = 13.73 min.

E. General procedure for the synthesis of compounds 4/4′

This compound was prepared according to literature procedure.[24]

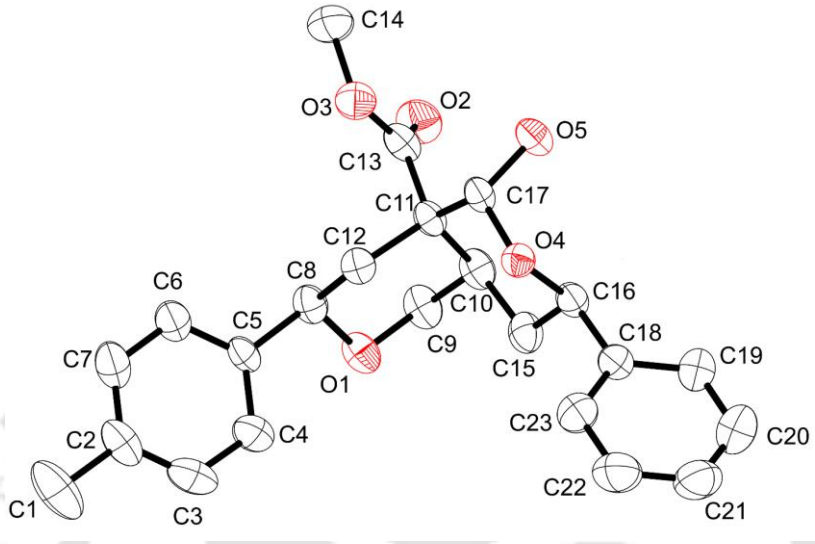
To a stirred solution of pure *cis*-compound **3a** (0.1mmol) in DMSO (0.5 mL), LiCl (3 equiv.) and 1 drop of H_2O was added to it and then the reaction mixture was placed on an oil bath at 110 °C for 48 hours. Next the reaction mixture was diluted with water and the mixture was extracted with ethyl acetate. The organic layer was dried with Na_2SO_4 and concentrated in *vacuo* and the residue was purified by flash column chromatography to obtain the desired product.

F. General procedure for the synthesis of compounds 5/5′ and 6

To a stirred solution of pure *cis*-compound **3a** (0.1 mmol) in MeOH at 0 °C, $NaBH_4$ (2 equiv.) was added. After stirring for 5-6 hours at room temperature, the reaction mixture was poured into ice water and extracted with ethyl acetate. The product was purified by

flash column chromatography using ethyl acetate and hexane (15%) as an eluent to get the desired product.

Crystal structure of compound 6



ORTEP crystal structure

Table 1. Crystal data and structure refinement for compound 6

Parameters	6
CCDC No.	1487919
Formula	C_{23} H_{26} O_5
Fw	382.44
Crystal system	triclinic
Space group	P-1
a/Å	6.1090(6)
b/Å	11.7023(11)
c/Å	15.2943(13)
α/°	77.031(7)
β/°	84.147(7)
γ/°	76.437(7)
V/Å^3	1034.37(17)
Z	2

D_c/g cm^{-3}	1.228
μ Mo $K_α$/mm^{-1}	0.086
F000	408.0
T/K	298(2)
θ max.	17.61
Total no. of reflections	7952
Independent reflections	3223
Observed reflections	1352
Parameters refined	256
R_1, I > 2σ(I)	0.0648
wR_2, I > 2σ(I)	0.1422
GOF (F^2)	0.984

3.7 References

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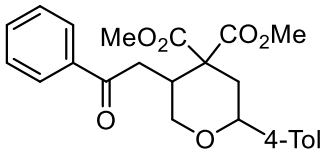
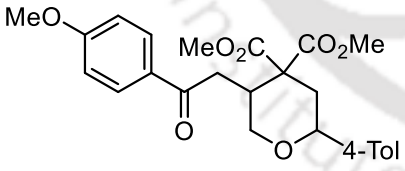
3.8 Characterization Data of Products

2-(dimethyl-tetrahydro-6-p-tolylpyran-4,4-dicarboxylate-3-yl)-1-phenylethanone (3a/3a')



This compound was prepared according to the general procedure C. Reaction was completed after 24 h. Analytical TLC on silica gel using 10% ethyl acetate/hexane. White semi solid (35 mg, yield: 85%); **Diastereomeric ratio:** 2:1; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.00 (dd, *J* = 16.7, 7.8 Hz, 3H), 7.58 (t, *J* = 7.3 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 3H), 7.26 (t, *J* = 7.9 Hz, 2H), 7.16 (t, *J* = 8.5 Hz, 3H), 4.56 (d, *J* = 11.5 Hz, 0.5H), 4.27 (d, *J* = 11.8 Hz, 1H), 4.05 - 3.95 (m, Hz, 3H), 3.86 (s, 5H), 3.70 (t, *J* = 11.5 Hz, 0.6H), 3.67 (s, 3H), 3.64 (s, 2H), 3.61 – 3.51 (m, 2H), 3.35 (d, *J* = 8.8 Hz, 1H), 3.14 – 3.07 (m, 0.5H), 2.94 (dd, *J* = 17.9, 8.6 Hz, 0.5H), 2.82 (d, *J* = 17.5 Hz, 1H), 2.48 (d, *J* = 14.3 Hz, 1H), 2.34 (s, 3H), 2.33 (s, 2H), 2.24 (t, *J* = 13.8 Hz, 1H), 2.15 (t, *J* = 13.8 Hz, 0.6H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 198.2, 198.0, 171.2, 170.9, 170.8, 170.7, 138.7, 137.7, 137.7, 137.2, 136.9, 133.5, 133.4, 129.3, 128.8, 128.8, 128.4, 128.3, 126.0, 125.9, 76.5, 75.9, 69.3, 68.79, 57.1, 56.9, 53.3, 53.2, 53.0, 52.7, 40.4, 37.4, 36.9, 36.3, 34.2, 33.0, 21.3; **FT-IR (thin film):** 1721, 1677, 1449, 1227, 1088, 813, 758, 691 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{24}H_{27}O_6$ $[M+H]^+$ 411.1802; found: 411.1806.

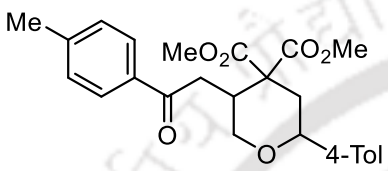
1-(4-methoxyphenyl)-2-(dimethyl-tetrahydro-6-p-tolylpyran-4,4-dicarboxylate-3-yl) ethanone (3b/3b')



This compound was prepared according to the general procedure C. Reaction was completed after 24 h. Analytical TLC on silica gel using 15% ethyl acetate/hexane. Colorless oil (41 mg, yield: 93%); **Diastereomeric ratio:** 2.2:1; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.99 (dd, *J* = 21.4, 8.6 Hz, 3H), 7.26 (t, *J* = 9.5 Hz, 3H), 7.19 – 7.06 (m, 4H), 6.94 (d, *J* = 8.4 Hz, 3H), 4.57 (d, *J* = 11.4 Hz, 0.5H), 4.26 (d, *J* = 11.8 Hz, 1H), 4.04 – 3.93 (m, 3H), 3.87 (s, 4H), 3.86 (s, 5H), 3.74 – 3.68 (m, 1H), 3.66 (s, 3H), 3.64 (s, 2H), 3.49 (dd, *J* = 17.2, 9.5 Hz, 2H), 3.33 (d, *J* = 8.9 Hz, 1H), 3.08 - 3.06 (m, 0.5H), 2.86 (dd, *J* = 17.5, 8.8 Hz, 0.5H), 2.73 (d, *J* = 17.1 Hz, 1H), 2.47 (d, *J* = 14.5 Hz, 2H), 2.34 (s, 3H), 2.33 (s, 1H), 2.23 (t, *J* = 13.8 Hz, 1H), 2.13 (t, *J* = 13.2 Hz, 0.7H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 196.8, 196.5, 171.2, 170.9,

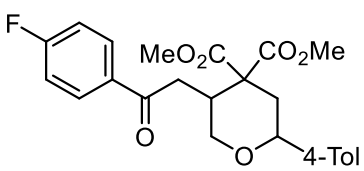
170.8, 170.7, 163.8, 163.8, 138.8, 137.7, 130.7, 130.6, 130.4, 129.5, 129.3, 127.3, 126.0, 125.9, 114.0, 113.9, 76.5, 75.9, 69.3, 68.8, 57.2, 57.0, 55.7, 53.2, 53.1, 52.9, 52.6, 40.5, 37.2, 37.1, 36.6, 36.4, 34.3, 33.2, 21.3; **FT-IR (thin film):** 1733, 1678, 1600, 1575, 1511, 1435, 1254, 1081, 1029, 815, 736 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{25}H_{29}O_7$ $[M+H]^+$ 441.1908; found: 441.1906.

1-p-tolyl-2-(dimethyl-tetrahydro-6-p-tolylpyran-4,4-dicarboxylate-3-yl)ethanone (3c/3c')



This compound was prepared according to the general procedure C. Reaction was completed after 36 h. Analytical TLC on silica gel using 10% ethyl acetate/hexane. Colorless oil (27 mg, yield: 64%); **Diastereomeric ratio:** 2.4:1; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.90 (dd, *J* = 16.9, 7.9 Hz, 3H), 7.26 (t, *J* = 8.4 Hz, 5H), 7.16 (t, *J* = 7.8 Hz, 3H), 4.56 (d, *J* = 11.5 Hz, 0.5H), 4.26 (d, *J* = 11.8 Hz, 1H), 4.04 - 3.94 (m, 2H), 3.86 (s, 4H), 3.70 (t, *J* = 11.6 Hz, 0.5H), 3.66 (s, 3H), 3.64 (s, 1H), 3.55 – 3.49 (m, 2H), 3.34 (d, *J* = 9.0 Hz, 1H), 3.12 - 3.07 (m, 0.5H), 2.91 (dd, *J* = 17.8, 8.6 Hz, 0.5H), 2.77 (d, *J* = 17.2 Hz, 1H), 2.47 (d, *J* = 14.3 Hz, 1H), 2.42 (s, 4H), 2.35 (s, 3H), 2.33 (s, 1H), 2.23 (t, *J* = 13.2 Hz, 1H), 2.14 (t, *J* = 12.6 Hz, 0.5H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 197.9, 197.6, 171.2, 170.9, 170.8, 170.7, 144.3, 144.2, 138.8, 137.7, 137.6, 134.7, 134.5, 129.5, 129.4, 129.3, 128.5, 128.4, 126.0, 125.9, 76.49, 75.92, 69.34, 68.8, 57.1, 56.9, 53.3, 53.2, 52.9, 52.7, 40.5, 37.2, 36.7, 36.4, 34.2, 33.0, 21.8, 21.3; **FT-IR (thin film):** 1733, 1683, 1607, 1434, 1241, 1178, 1087, 1036, 810 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{25}H_{29}O_6$ $[M+H]^+$ 425.1959; found: 425.1959.

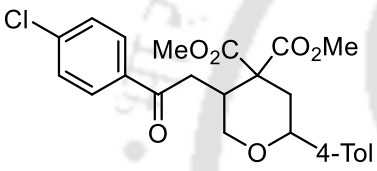
1-(4-fluorophenyl)-2-(dimethyl-tetrahydro-6-p-tolylpyran-4,4-dicarboxylate-3-yl) ethanone (3d/3d')



This compound was prepared according to the general procedure C. Reaction was completed after 24 h. Analytical TLC on silica gel using 12% ethyl acetate/hexane. Colorless oil (28 mg, yield: 65%); **Diastereomeric ratio:** 2:1; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.08 –7.99 (m, 3H), 7.26 (t, *J* = 7.8 Hz, 2H), 7.15 (dd, *J* = 18.9, 9.9 Hz, 6H), 4.57 (d, *J* = 11.5 Hz, 0.5H), 4.27 (d, *J* =

11.8 Hz, 1H), 3.99 (m, 3H), 3.86 (s, 4H), 3.71 (t, *J* = 9.6 Hz, 0.6H), 3.67 (s, 3H), 3.65 (s, 2H), 3.58 – 3.48 (m, 2H), 3.33 (d, *J* = 8.8 Hz, 1H), 3.09 – 3.06 (m, 0.6H), 2.88 (dd, *J* = 17.8, 8.7 Hz, 0.6H), 2.79 (d, *J* = 17.2 Hz, 1H), 2.48 (d, *J* = 14.2 Hz, 1H), 2.35 (s, 3H), 2.33 (s, 2H), 2.22 (t, *J* = 13.2 Hz, 1H), 2.13 (t, *J* = 13.2 Hz, 0.6H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 196.7, 196.4, 171.2, 170.9, 170.7, 166.1 (d, *J* = 256.5 Hz), 138.7, 138.6, 137.8, 137.7, 133.7, 133.4, 131.1 (d, *J* = 9.0 Hz), 130.9 (d, *J* = 9.0 Hz), 129.3, 126.0, 125.9, 116.0 (d, *J* = 6.0 Hz), 115.9 (d, *J* = 7.5 Hz), 76.5, 76.0, 69.4, 68.8, 57.1, 56.9, 53.3, 53.2, 53.0, 52.7, 40.5, 37.4, 36.9, 36.5, 34.2, 33.1, 21.3; **FT-IR (thin film):** 1732, 1688, 1599, 1434, 1239, 1157, 1086, 815, 668 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{24}H_{26}FO_6$ $[M+H]^+$ 429.1708; found: 429.1708.

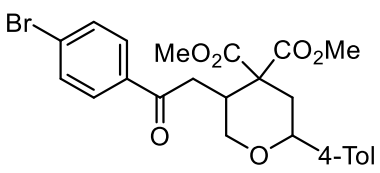
1-(4-chlorophenyl)-2-(dimethyl-tetrahydro-6-p-tolylpyran-4,4-dicarboxylate-3-yl) ethanone (3e/3e')



This compound was prepared according to the general procedure C. Reaction was completed after 16 h. Analytical TLC on silica gel using 12% ethyl acetate/hexane. Colorless oil (27 mg, yield: 61%); **Diastereomeric ratio:** 1.9:1; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.94 (dd, *J* = 21.2, 8.3 Hz, 3H), 7.45 (d, *J* = 8.3 Hz, 3H), 7.26 (t, *J* = 7.5 Hz, 2H), 7.16 (t, *J* = 7.2 Hz, 4H), 4.56 (d, *J* = 11.5 Hz, 0.5H), 4.27 (d, *J* = 11.8 Hz, 1H), 4.02 - 3.92 (m, 3H), 3.86 (s, 4H), 3.73 (d, *J* = 14.0 Hz, 2H), 3.67 (s, 3H), 3.64 (s, 2H), 3.57 – 3.46 (m, 2H), 3.33 (d, *J* = 8.8 Hz, 1H), 3.08 – 3.05 (m, 0.6H), 2.88 (dd, *J* = 17.9, 8.6 Hz, 0.6H), 2.80 (d, *J* = 16.7 Hz, 1H), 2.48 (d, *J* = 14.1 Hz, 1H), 2.35 (s, 3H), 2.33 (s, 2H), 2.22 (t, *J* = 13.2, 1H), 2.13 (t, *J* = 12.6 Hz, 0.6H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 197.1, 196.9, 171.1, 170.9, 170.7, 139.9, 139.9, 138.7, 137.8, 135.5, 135.3, 129.9, 129.7, 129.4, 129.3, 129.2, 129.1, 126.7, 126.0, 125.9, 76.5, 75.9, 69.3, 68.7, 57.1, 56.9, 53.3, 53.2, 53.0, 52.7, 40.4, 37.4, 36.9, 36.4, 34.2, 33.0, 21.3; **FT-IR(thin film):** 1733, 1688, 1589, 1434, 1242, 1091, 1036, 814 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{24}H_{26}ClO_6$ $[M+H]^+$ 445.1412; found: 445.1415.

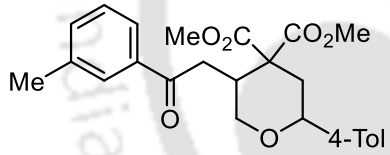
1-(4-bromophenyl)-2-(dimethyl tetrahydro-6-p-tolylpyran-4,4-dicarboxylate-3-yl) ethanone (3f/3f')

This compound was prepared according to the general procedure C. Reaction was completed after 24 h. Analytical TLC on silica gel using 12% ethyl acetate/hexane.



Colorless oil (39 mg, yield: 79%); **Diastereomeric ratio:** 1.6:1; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.87 (dd, *J* = 14.0, 8.4 Hz, 3H), 7.61 (d, *J* = 8.3 Hz, 3H), 7.26 (t, *J* = 6.3 Hz, 2H), 7.16 (t, *J* = 7.3 Hz, 4H), 4.56 (d, *J* = 10.9 Hz, 0.6H), 4.27 (d, *J* = 10.8 Hz, 1H), 4.03 – 3.86 (m, 3H), 3.86 (s, 3H), 3.86 (s, 2H), 3.72 (t, *J* = 10.7 Hz, 1H), 3.66 (s, 3H), 3.64 (s, 2H), 3.58 - 3.45 (m, 2H), 3.33 (d, *J* = 8.4 Hz, 1H), 3.10 - 3.03 (m, 0.6H), 2.91 – 2.78 (m, 2H), 2.48 (d, *J* = 14.1 Hz, 2H), 2.34 (s, 3H), 2.33 (s, 2H), 2.22 (t, *J* = 13.2 Hz, 1H), 2.13 (t, *J* = 12.8 Hz, 0.6H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 197.3, 197.1, 171.1, 170.9, 170.7, 138.6, 137.8, 137.7, 135.9, 135.6, 132.2, 132.1, 130.0, 129.8, 129.3, 128.7, 126.7, 126.0, 125.9, 76.5, 76.0, 69.3, 68.72, 57.1, 56.8, 53.3, 53.2, 53.0, 52.7, 40.4, 37.4, 36.9, 36.4, 34.2, 33.0, 21.35; **FT-IR (thin film):** 1731, 1688, 1585, 1240, 1070, 1007, 814 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{24}H_{26}BrO_6$ $[M+H]^+$ 489.0907; found: 489.0909.

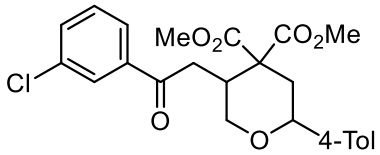
1-m-tolyl-2-(dimethyl tetrahydro-6-p-tolylpyran-4,4-dicarboxylate-3-yl) ethanone (3g/3g')



This compound was prepared according to the general procedure C. Reaction was completed after 36 h. Analytical TLC on silica gel using 10% ethyl acetate/hexane. Colorless oil (30 mg, yield: 71%); **Diastereomeric ratio:** 1.8:1; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.80 (d, *J* = 11.1 Hz, 3H), 7.41 – 7.33 (m, 3H), 7.27 (t, *J* = 7.4 Hz, 2H), 7.16 (t, *J* = 7.2 Hz, 3H), 4.55 (d, *J* = 11.3 Hz, 0.5H), 4.27 (d, *J* = 11.3 Hz, 1H), 4.04 – 3.96 (m, 2H), 3.86 (s, 4H), 3.72 (d, *J* = 11.4 Hz, 0.5H), 3.67 (s, 3H), 3.65 (s, 1H), 3.53 (dd, *J* = 17.7, 9.4 Hz, 2H), 3.34 (d, *J* = 9.3 Hz, 1H), 3.12 – 3.07 (m, 0.6H), 2.94 (dd, *J* = 17.9, 8.6 Hz, 0.6H), 2.79 (d, *J* = 17.7 Hz, 1H), 2.48 (d, *J* = 14.2 Hz, 2H), 2.43 (s, 4H), 2.35 (s, 3H), 2.34 (s, 2H), 2.24 (t, *J* = 12.4 Hz, 1H), 2.16 (t, *J* = 12.0 Hz, 0.6H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 198.4, 198.2, 171.2, 171.0, 170.8, 170.7, 138.7, 138.6, 138.6, 137.7, 137.6, 137.2, 136.9, 134.2, 134.1, 129.3, 128.9, 128.8, 128.7, 128.6, 126.0, 125.9, 125.6, 125.5, 76.5, 75.9, 69.3, 68.8, 57.1, 56.9, 53.3, 53.2, 53.0, 52.7, 40.5, 37.4, 36.9, 36.4, 34.2, 33.0, 21.6, 21.4; **FT-IR (thin film):** 1733, 1684, 1434, 1242,

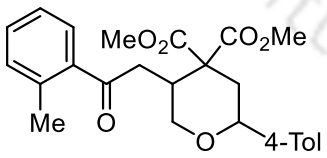
1177, 1087, 814, 690 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{25}H_{29}O_6$ $[M+H]^+$ 425.1959; found: 425.1959.

1-(3-chlorophenyl)-2-(dimethyl tetrahydro-6-p-tolylpyran-4,4-dicarboxylate-3-yl) ethanone (3h/3h')



This compound was prepared according to the general procedure C. Reaction was completed after 24 h. Analytical TLC on silica gel using 12% ethyl acetate/hexane. Sticky solid (37 mg, yield: 83%); **Diastereomeric ratio:** 1.6:1; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.96 (d, *J* = 16.5 Hz, 2H), 7.88 (dd, *J* = 21.2, 7.7 Hz, 2H), 7.55 (d, *J* = 7.8 Hz, 2H), 7.42 (t, *J* = 7.8 Hz, 2H), 7.26 (t, *J* = 9.3 Hz, 3H), 7.17 (t, *J* = 9.3 Hz, 3H), 4.55 (d, *J* = 11.5 Hz, 0.7H), 4.28 (d, *J* = 11.8 Hz, 1H), 4.03 – 3.92 (m, 3H), 3.86 (s, 5H), 3.72 (t, *J* = 14.4 Hz, 1H), 3.68 (s, 3H), 3.66 (s, 2H), 3.57 – 3.46 (m, 2H), 3.33 (d, *J* = 8.6 Hz, 1H), 3.09 – 3.06 (m, 0.7H), 2.90 (dd, *J* = 18.0, 8.5 Hz, 0.7H), 2.82 (d, *J* = 17.6 Hz, 1H), 2.49 (d, *J* = 14.1 Hz, 2H), 2.34 (s, 3H), 2.33 (s, 2H), 2.22 (t, *J* = 13.2 Hz, 1H), 2.17 – 2.11 (m, 0.7H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 197.0, 196.8, 171.1, 170.8, 170.7, 170.7, 138.7, 138.6, 138.5, 137.8, 137.7, 135.2, 135.2, 133.4, 133.3, 130.2, 130.2, 129.3, 128.5, 128.4, 126.5, 126.4, 126.0, 125.9, 76.5, 76.0, 69.3, 68.7, 57.1, 56.9, 53.3, 53.2, 53.0, 52.7, 40.4, 37.5, 37.1, 36.3, 34.18, 33.0, 21.3; **FT-IR (thin film):** 1735, 1690, 1432, 1243, 1080, 813, 791 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{24}H_{26}ClO_6$ $[M+H]^+$ 445.1412; found: 445.1417.

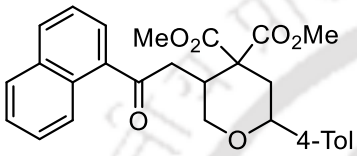
1-o-tolyl-2-(dimethyl tetrahydro-6-p-tolylpyran-4,4-dicarboxylate-3-yl) ethanone (3i/3i')



This compound was prepared according to the general procedure C. Reaction was completed after 40 h. Analytical TLC on silica gel using 10% ethyl acetate/hexane. Colorless oil (25 mg, yield: 59%); **Diastereomeric ratio:** 2.1:1; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.69 (dd, *J* = 13.7, 7.8 Hz, 1H), 7.38 (t, *J* = 7.4 Hz, 1H), 7.27 (dd, *J* = 18.2, 7.2 Hz, 5H), 7.16 (d, *J* = 7.1 Hz, 3H), 4.58 (d, *J* = 11.5 Hz, 0.5H), 4.27 (d, *J* = 11.8 Hz, 1H), 4.03 – 3.97 (m, 3H), 3.86 (s, 3H), 3.84 (s, 1H), 3.69 (s, 3H), 3.67 (s, 2H), 3.52 – 3.43 (m, 2H), 3.32 (d, *J* = 9.1 Hz, 1H), 3.08 - 3.05 (m, 0.5H), 2.82 (dd, *J* = 18.1, 8.7 Hz, 0.5H), 2.75 (d, *J* = 17.6 Hz, 1H), 2.50 (s, 4H), 2.45 (d, *J* = 14.5 Hz, 1H), 2.34 (s, 4H), 2.18 (t, *J* =

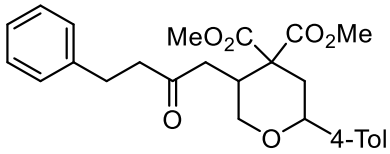
13.2Hz, 1H), 2.12 (t, *J* = 12.6 Hz, 0.6H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 202.3, 202.1, 171.2, 170.9, 170.78, 170.7, 138.8, 138.7, 138.3, 138.2, 137.7, 137.6, 132.2, 131.6, 129.3, 128.7, 128.6, 126.00, 125.9, 76.6, 75.9, 69.4, 68.8, 57.1, 56.9, 53.2, 53.1, 53.0, 52.3, 40.5, 40.3, 40.0, 36.5, 34.3, 33.1, 21.5, 21.4, 21.3; **FT-IR (thin film):** 1733, 1687, 1435, 1240. 1086, 1035, 815, 758 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{25}H_{29}O_6$ $[M+H]^+$ 425.1959; found: 425.1960.

1-(naphthalen-1-yl)-2-(dimethyl tetrahydro-6-p-tolylpyran-4,4-dicarboxylate-3-yl) ethanone (3j/3j')



This compound was prepared according to the general procedure C. Reaction was completed after 24 h. Analytical TLC on silica gel using 12% ethyl acetate/hexane. Sticky solid (33 mg, yield: 72%); **Diastereomeric ratio:** 1.5:1; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.59 (t, *J* = 8.4 Hz, 1H), 7.95 (ddd, *J* = 22.4, 16.2, 8.1 Hz, 5H), 7.62 – 7.51 (m, 5H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.17 (dd, *J* = 8.0, 4.5 Hz, 3H), 4.61 (d, *J* = 10.1 Hz, 0.7H), 4.31 (d, *J* = 10.2 Hz, 1H), 4.14 – 4.05 (m, 2H), 3.88 (s, 3H), 3.85 (s, 2H), 3.75 (dd, *J* = 15.3, 7.4 Hz, 1H), 3.70 (s, 3H), 3.68 (s, 2H), 3.62 (t, *J* = 8.4 Hz, 0.5H), 3.43 (d, *J* = 9.4 Hz, 1H), 3.21 - 3.14 (m, 0.7H), 3.01 – 2.90 (m, 2H), 2.53 – 2.47 (m, 2H), 2.35 (s, 3H), 2.34 (s, 2H), 2.26 – 2.13 (m, 2H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 202.5, 202.4, 171.2, 170.9, 170.8, 170.7, 138.7, 138.7, 137.8, 137.7, 136.3, 135.7, 134.1, 133.0, 132.9, 130.3, 130.2, 129.3, 128.7, 128.6, 128.2, 128.1, 128.0, 127.8, 126.7, 126.6, 126.0, 125.9, 125.8, 125.8, 124.6, 124.5, 76.6, 75.9, 69.4, 68.8, 57.1, 56.8, 53.3, 53.2, 53.0, 52.7, 40.8, 40.6, 40.5, 36.7, 34.3, 33.4, 21.3; **FT-IR (thin film):** 1726, 1682, 1432, 1241, 1174, 1082, 799, 771 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{28}H_{29}O_6$ $[M+H]^+$ 461.1959; found: 461.1958.

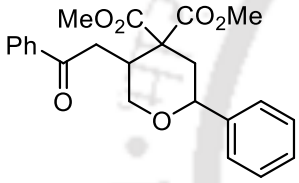
2-(dimethyl-tetrahydro-6-p-tolylpyran-4,4-dicarboxylate-3-yl)4-phenylbutan-2-one (3k/3k')



This compound was prepared according to the general procedure C. Reaction was completed after 24 h. Analytical TLC on silica gel using 12% ethyl acetate/hexane. Colorless oil (21 mg, yield: 48%); **Diastereomeric ratio:** 1.1:1; **^{1}H**

NMR (400 MHz, $CDCl_3$): δ 7.30 – 7.26 (m, 3H), 7.23 (dd, *J* = 8.0, 3.9 Hz, 5H), 7.19 – 7.14 (m, 9H), 4.51 (d, *J* = 10.5 Hz, 1H), 4.20 (d, *J* = 10.6 Hz, 1H), 3.89 (dd, *J* = 11.6, 4.6 Hz, 2H), 3.83 (s, 3H), 3.80 (s, 3H), 3.64 (s, 3H), 3.63 (s, 3H), 3.55 (dd, *J* = 14.3, 9.0 Hz, 1H), 3.15 - 3.12 (m, 1H), 2.98 – 2.89 (m, 6H), 2.78 – 2.72 (m, 4H), 2.44 – 2.36 (m, 3H), 2.34 (s, 3H), 2.33 (s, 3H), 2.13 – 2.03 (m, 2H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 208.0, 207.7, 171.1, 170.8, 170.7, 170.6, 141.1, 141.0, 138.7, 138.6, 137.8, 137.7, 129.3, 128.7, 128.5, 128.5, 126.3, 126.0, 125.9, 76.5, 75.9, 69.4, 68.6, 56.8, 56.6, 53.3, 53.2, 53.0, 52.7, 44.9, 44.5, 41.5, 41.4, 40.3, 35.8, 34.0, 32.5, 30.0, 21.4; **FT-IR (thin film):** 1732, 1434, 1241, 1084, 816, 750, 700 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{26}H_{31}O_6$ $[M+H]^+$ 439.2115; found: 439.2117.

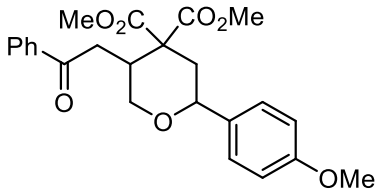
2-(dimethyl-tetrahydro-6-phenylpyran-4,4-dicarboxylate-3-yl)-1-phenylethanone (3l/3l')



This compound was prepared according to the general procedure C. Reaction was completed after 16 h. Analytical TLC on silica gel using 10% ethyl acetate/hexane. Colorless oil (16 mg, yield: 40%); **Diastereomeric ratio:** 2:1; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.00 (dd, *J* = 17.0, 7.5 Hz, 3H), 7.58 (t, *J* = 7.3 Hz, 2H), 7.48 (t, *J* = 7.5 Hz, 3H), 7.26 (t, *J* = 7.7 Hz, 3H), 7.16 (t, *J* = 8.4 Hz, 3H), 4.56 (d, *J* = 11.4 Hz, 0.7H), 4.27 (d, *J* = 11.8 Hz, 1H), 4.04 – 3.95 (m, 3H), 3.86 (s, 5H), 3.70 (t, *J* = 11.5 Hz, 1H), 3.67 (s, 3H), 3.64 (s, 2H), 3.59 – 3.52 (m, 2H), 3.35 (d, *J* = 8.8 Hz, 1H), 3.12 – 3.09 (m, 0.7H), 2.94 (dd, *J* = 18.0, 8.6 Hz, 0.7H), 2.81 (d, *J* = 17.7 Hz, 1H), 2.48 (d, *J* = 14.1 Hz, 2H), 2.35 (s, 3H), 2.34 (s, 2H), 2.24 (t, *J* = 12.6 1H), 2.15 (t, *J* = 13.2 Hz, 0.8H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 198.2, 198.0, 171.1, 170.9, 170.8, 170.7, 141.7, 137.2, 136.9, 133.5, 133.4, 128.9, 128.8, 128.7, 128.4, 128.3, 128.1, 128.0, 126.1, 126.0, 76.7, 76.1, 69.4, 68.8, 57.1, 56.9, 53.6, 53.3, 53.2, 53.0, 52.7, 40.5, 37.4, 36.9, 36.4, 34.3, 33.0; **FT-IR (thin film):** 1734, 1685, 1452, 1263, 1088, 1026, 736, 703 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{23}H_{25}O_6$ $[M+H]^+$ 397.1646; found: 397.1647.

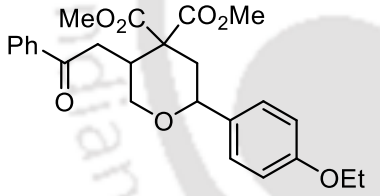
2-(dimethyl tetrahydro-6-(4-methoxyphenyl)-4,4-dicarboxylate-3-yl)-1-phenylethanone (3m/3m')

This compound was prepared according to the general procedure C. Reaction was completed after 7 h. Analytical TLC on silica gel using 15% ethyl acetate/hexane.



Colorless oil (30 mg, yield: 70%); **Diastereomeric ratio:** 1.7:1; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.00 (t, J = 9.6 Hz, 3H), 7.58 (t, *J* = 7.1 Hz, 2H), 7.47 (t, *J* = 7.5 Hz, 3H), 7.30 (t, *J* = 6.7 Hz, 3H), 6.89 (t, *J* = 6.8 Hz, 3H), 4.54 (d, *J* = 11.7 Hz, 0.6H), 4.25 (d, *J* = 11.9 Hz, 1H), 4.04 – 3.93 (m, 3H), 3.86 (s, 4H), 3.80 (s, 5H), 3.73 (t, *J* = 9.4 Hz, 1H), 3.67 (s, 3H), 3.65 (s, 2H), 3.60 – 3.51 (m, 2H), 3.35 (d, *J* = 9.1 Hz, 1H), 3.14 – 3.08 (m, 0.6H), 2.94 (dd, *J* = 17.9, 8.6 Hz, 0.6H), 2.82 (d, *J* = 17.8 Hz, 1H), 2.47 (d, *J* = 14.1 Hz, 2H), 2.25 (t, *J* = 13.6 Hz, 1H), 2.16 (t, *J* = 12.8 Hz, 0.6H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 198.2, 197.9, 171.1, 170.9, 170.7, 170.6, 159.4, 159.3, 137.1, 136.83, 133.8, 133.7, 133.5, 133.4, 128.8, 128.7, 128.3, 128.2, 127.4, 127.3, 114.0, 76.3, 75.7, 69.4, 68.8, 57.1, 56.8, 55.5, 53.3, 53.2, 53.0, 52.7, 40.4, 37.3, 36.9, 36.3, 34.1, 32.9; **FT-IR (thin film):** 1730, 1689, 1611, 1517, 1452, 1247, 1084, 1034, 870, 752 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{24}H_{27}O_7$ $[M+H]^+$ 427.1751; found: 427.1752.

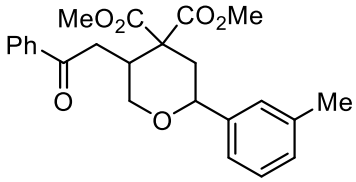
2-(dimethyl tetrahydro-6-(4-ethoxyphenyl)-4,4-dicarboxylate-3-yl)-1-phenylethanone (3n/3n')



This compound was prepared according to the general procedure C. Reaction was completed after 3 h. Analytical TLC on silica gel using 15% ethyl acetate/hexane. Colorless oil (19 mg, yield: 43%); **Diastereomeric ratio:** 1.9:1; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.00 (dd, *J* = 16.5, 7.6 Hz, 3H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 3H), 7.29 (t, *J* = 8.8 Hz, 3H), 6.87 (t, *J* = 8.8 Hz, 3H), 4.53 (d, *J* = 10.4 Hz, 0.6H), 4.24 (d, *J* = 10.4 Hz, 1H), 4.05 – 4.00 (m, 4H), 3.96 (t, *J* = 13.4 Hz, 2H), 3.86 (s, 3H), 3.85 (s, 2H), 3.70 (t, *J* = 11.5 Hz, 0.5H), 3.67 (s, 3H), 3.65 (s, 2H), 3.59 – 3.51 (m, 2H), 3.34 (d, *J* = 8.3 Hz, 1H), 3.13 – 3.07 (m, 0.6H), 2.94 (dd, *J* = 18.0, 8.6 Hz, 0.6H), 2.82 (d, *J* = 15.8 Hz, 1H), 2.46 (d, *J* = 14.3 Hz, 2H), 2.25 (t, *J* = 12.6 Hz, 1H), 2.16 (t, *J* = 12.0 Hz, 0.6H), 1.40 (td, *J* = 7.0, 3.5 Hz, 6H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 198.2, 198.0, 171.2, 170.9, 170.8, 170.7, 158.8, 158.7, 137.2, 136.9, 133.8, 133.7, 133.5, 133.4, 128.9, 128.8, 128.4, 128.3, 127.4, 127.3, 114.6, 76.34, 75.74, 69.4, 68.9, 63.7, 57.1, 56.9, 53.3, 53.2, 53.0, 52.7, 40.4, 37.4, 36.9, 36.4, 34.1, 32.9, 15.0; **FT-**

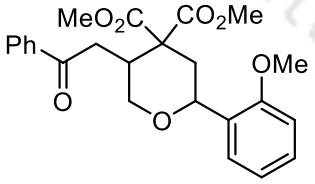
IR (thin film): 1734, 1686, 1613, 1514, 1448, 1245, 1176, 1085, 1046, 825, 754, 690 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{25}H_{29}O_7$ $[M+H]^+$ 441.1908; found: 441.1906.

2-(dimethyltetrahydro-6-m-tolylpyran-4,4-dicarboxylate-3-yl)-1-phenylethanone (3o/3o′)



This compound was prepared according to the general procedure C. Reaction was completed after 24 h. Analytical TLC on silica gel using 10% ethyl acetate/hexane. Colorless oil (15 mg, yield: 36%); **Diastereomeric ratio:** 1.8:1; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.01 (t, *J* = 9.1 Hz, 3H), 7.58 (t, *J* = 7.4 Hz, 2H), 7.48 (t, *J* = 7.6 Hz, 3H), 7.24 (d, *J* = 7.6 Hz, 1H), 7.24 – 7.14 (m, 4H), 7.10 (t, *J* = 6.8 Hz, 2H), 4.57 (d, *J* = 11.4 Hz, 0.6H), 4.27 (d, *J* = 11.4 Hz, 1H), 4.06 – 3.98 (m, 3H), 3.87 (s, 4H), 3.72 (d, *J* = 11.5 Hz, 0.7H), 3.67 (s, 3H), 3.65 (s, 2H), 3.61 – 3.51 (m, 2H), 3.36 (d, *J* = 9.6 Hz, 1H), 3.15 – 3.08 (m, 0.7H), 2.94 (dd, *J* = 17.9, 8.8 Hz, 0.7H), 2.83 (d, *J* = 17.6 Hz, 1H), 2.49 (d, *J* = 14.0 Hz, 2H), 2.37 (s, 3H), 2.35 (s, 2H), 2.24 (t, *J* = 12.0 Hz, 1H), 2.17 (t, *J* = 6.8 Hz, 0.7H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 198.2, 198.0, 171.2, 170.9, 170.8, 170.7, 141.6, 141.5, 138.4, 137.2, 136.9, 133.5, 133.4, 128.9, 128.8, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 126.8, 126.7, 123.2, 123.1, 76.7, 76.1, 69.4, 68.8, 57.1, 56.9, 53.3, 53.2, 53.0, 52.7, 40.5, 37.4, 36.9, 36.4, 34.2, 33.0, 21.7, 21.6; **FT-IR (thin film):** 1730, 1685, 1452, 1239, 1084, 1034, 785, 756 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{24}H_{27}O_6$ $[M+H]^+$ 411.1802; found: 411.1803.

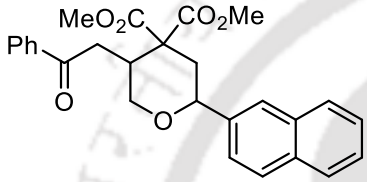
2-(dimethyl tetrahydro-6-(2-methoxyphenyl)-4,4-dicarboxylate-3-yl)-1-phenylethanone (3p/3p′)



This compound was prepared according to the general procedure C. Reaction was completed after 14 h. Analytical TLC on silica gel using 15% ethyl acetate/hexane. Sticky solid (29 mg, yield: 68%); **Diastereomeric ratio:** 1:1.3; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.01 (t, *J* = 8.0 Hz, 3H), 7.58 (dd, *J* = 11.5, 6.7 Hz, 2H), 7.48 (dd, *J* = 13.2, 6.5 Hz, 5H), 7.24 (t, *J* = 8.0 Hz, 2H), 6.99 (t, *J* = 7.5 Hz, 2H), 6.85 (t, *J* = 7.8 Hz, 2H), 4.88 (d, *J* = 11.1 Hz, 1H), 4.63 (d, *J* = 11.2 Hz, 0.8H), 4.05 (dd, *J* = 11.4, 4.8 Hz, 2H), 3.97 (d, *J* = 12.4 Hz, 0.8H), 3.88 (s, 5H), 3.81 (s, 6H), 3.66 (s, 2H), 3.62 (s, 4H), 3.57 (dd, *J* = 10.4, 7.1 Hz, 1H), 3.33 (d, *J* = 9.5 Hz, 0.8H), 3.12 – 3.06 (m, 1H),

3.01 (dd, *J* = 17.8, 8.2 Hz, 1H), 2.77 (d, *J* = 17.6 Hz, 0.5H), 2.62 – 2.52 (m, 2H), 2.15 – 1.99 (m, 2H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 198.3, 198.1, 171.2, 171.0, 170.9, 170.8, 155.9, 155.7, 137.2, 136.9, 133.4, 133.4, 130.3, 128.8, 128.7, 128.7, 128.5, 128.3, 128.2, 126.2, 126.1, 121.1, 120.9, 110.4, 110.2, 71.6, 70.5, 69.3, 69.0, 57.0, 56.9, 55.6, 53.1, 53.1, 52.8, 52.5, 39.2, 37.2, 36.9, 36.5, 33.2, 33.1; **FT-IR (thin film):** 1730, 1685, 1599, 1488, 1460, 1239, 1092, 1026, 752 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{24}H_{27}O_7$ $[M+H]^+$ 427.1751; found: 427.1754.

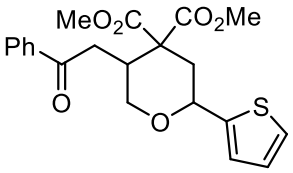
2-(dimethyl-tetrahydro-6-(naphthalen-3-yl)pyran-4,4-dicarboxylate-3-yl)-1-phenylethanone (3q/3q')



This compound was prepared according to the general procedure C. Reaction was completed after 20 h. Analytical TLC on silica gel using 12% ethyl acetate/hexane. Colorless oil (11 mg, yield: 25%); **Diastereomeric ratio:** 1.8:1; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.04 – 8.01 (m, 3H), 7.84 (t, *J* = 8.3 Hz, 7H), 7.59 (t, *J* = 8.0 Hz, 2H), 7.50 – 7.47 (m, 8H), 4.79 (d, *J* = 13.3 Hz, 0.6H), 4.48 (d, *J* = 10.1 Hz, 1H), 4.13 – 4.04 (m, 3H), 3.90 (s, 5H), 3.77 (t, *J* = 11.5 Hz, 1H), 3.68 (s, 3H), 3.66 (s, 2H), 3.63 – 3.55 (m, 2H), 3.41 (d, *J* = 9.1 Hz, 1H), 3.19 - 3.15 (m, 0.6H), 2.97 (dd, *J* = 17.9, 8.7 Hz, 0.7H), 2.87 (d, *J* = 14.4 Hz, 1H), 2.61 (d, *J* = 16.5 Hz, 2H), 2.32 (t, *J* = 14.4 Hz, 1H), 2.22 (t, *J* = 14.4 Hz, 8H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 198.2, 198.0, 171.1, 170.9, 170.7, 170.6, 139.2, 139.1, 137.2, 136.9, 133.5, 133.4, 133.4, 133.2, 128.9, 128.8, 128.4, 128.3, 128.2, 127.9, 126.4, 126.3, 126.2, 126.1, 124.8, 124.6, 124.2, 124.1, 76.7, 76.2, 69.2, 68.9, 57.2, 56.9, 53.4, 53.2, 53.03, 52.8, 40.6, 37.4, 37.0, 36.4, 34.3, 33.0; **FT-IR (thin film):** 1734, 1685, 1599, 1448, 1242, 1174, 1084, 818, 751, cm^{-1}; **HRMS (+ESI):** Calcd for $C_{27}H_{27}O_6$ $[M+H]^+$ 447.1802; found: 447.1804.

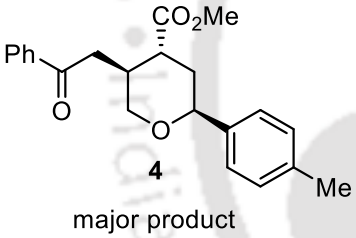
2-(dimethyl-tetrahydro-6-(thiophen-2-yl)pyran-4,4-dicarboxylate-3-yl)-1 phenylethanone (3r/3r')

This compound was prepared according to the general procedure C. Reaction was completed after 4 h. Analytical TLC on silica gel using 12% ethyl acetate/hexane.



Colorless oil (32 mg, yield: 79%); **Diastereomeric ratio:** 3.5:1; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.99 (dd, *J* = 14.6, 7.4 Hz, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 3H), 7.28 (t, *J* = 4.8 Hz, 1H), 7.04 (d, *J* = 3.4 Hz, 1H), 7.02 – 6.96 (m, 2H), 4.89 (d, *J* = 9.9 Hz, 0.3H), 4.56 (d, *J* = 10.1 Hz, 1H), 3.98 (dd, *J* = 29.4, 12.0 Hz, 2H), 3.85 (s, 3H), 3.84 (s, 1H), 3.73 (t, *J* = 11.2 Hz, 0.6H), 3.68 (s, 3H), 3.67 (s, 1H), 3.62 – 3.50 (m, 1H), 3.37 (d, *J* = 9.0 Hz, 1H), 3.14 - 3.07 (m, 0.3H), 2.91 (dd, *J* = 17.9, 8.5 Hz, 0.3H), 2.81 (d, *J* = 17.8 Hz, 1H), 2.64 (d, *J* = 13.9 Hz, 1H), 2.44 – 2.34 (m, 1H), 2.33 - 2.27 (m, 0.6H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 198.0, 197.8, 170.9, 170.7, 170.5, 170.4, 144.7, 144.6, 137.0, 136.7, 133.5, 133.4, 128.8, 128.3, 128.2, 126.7, 126.6, 125.2, 125.1, 124.1, 124.0, 72.6, 72.0, 69.3, 68.75, 56.8, 56.5, 53.4, 53.3, 53.1, 52.8, 40.0, 37.2, 36.7, 36.1, 33.9, 32.8; **FT-IR (thin film):** 1730, 1685, 1448, 1247, 1079, 1030, 752, 691 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{21}H_{23}O_6S$ $[M+H]^+$ 403.1210; found: 403.1212.

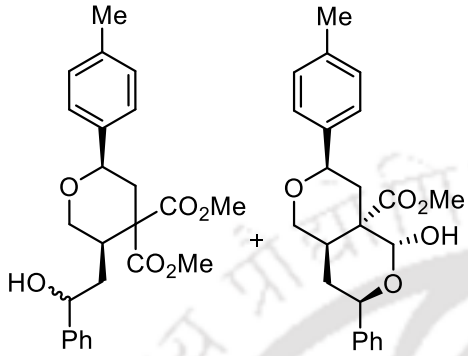
2-(methyl tetrahydro-6-p-tolylpyran-4-carboxylate-3-yl)-1-phenylethanone (4/4')



major product

This compound was prepared according to the general procedure E. Reaction was completed after 48 h. Analytical TLC on silica gel using 10% ethyl acetate/hexane. Colorless oil (26 mg, yield: 74%); **Diastereomeric ratio:** 2.7:1; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.00 (d, *J* = 7.9 Hz, 3H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.1 Hz, 3H), 7.27 (d, *J* = 7.8 Hz, 3H), 7.16 (d, *J* = 7.7 Hz, 3H), 4.59 (d, *J* = 10.5 Hz, 0.32H), 4.35 (d, *J* = 11.1 Hz, 1H), 4.09 (d, *J* = 11.9 Hz, 1H), 3.95 (d, *J* = 10.3 Hz, 0.42H), 3.84 – 3.80 (m, 1H), 3.78 (s, 1H), 3.66 (s, 3H), 3.52 (dd, *J* = 18.2, 10.0 Hz, 1H), 3.44 (dd, *J* = 17.4, 7.2 Hz, 0.45H), 3.21 (dd, *J* = 17.4, 6.5 Hz, 0.40H), 3.03 (d, *J* = 12.4 Hz, 1H), 2.93 (d, *J* = 16.8 Hz, 3H), 2.34 (s, 5H), 2.23 (d, *J* = 14.1 Hz, 1H), 2.05 – 1.93 (m, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 198.9, 174.7, 174.0, 139.2, 137.6, 137.3, 133.5, 133.3, 129.3, 128.9, 128.8, 128.3, 125.9, 79.3, 71.7, 52.1, 52.1, 44.4, 42.0, 40.1, 35.5, 31.2, 21.4; **HRMS (+ESI):** Calc for $C_{22}H_{25}O_4$ $[M+H]^+$ 353.1747; found: 353.1745.

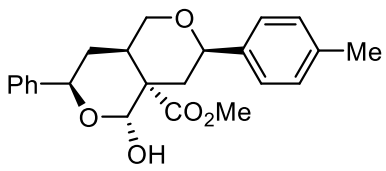
2-(dimethyl tetrahydro-6-p-tolylpyran-4,4-dicarboxylate-3-yl)-1-phenylethanol (5/5') and Methyl octahydro-5-hydroxy-7-phenyl-3-p-tolyl pyrano[4,3-c]pyran-4a-carboxylate (6)



5/5' **6**

This compound was prepared according to the general procedure. Reaction was completed after 5-6 h. Analytical TLC on silica gel using 15% ethyl acetate/hexane. White solid (24 mg, overall yield: 60%); **product ratio (5 and 6) =** 2:1; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.39 - 7.33 (m, 8H), 7.31 – 7.29 (m, 2H), 7.24 (d, *J* = 8.0 Hz, 3H), 7.15 (t, *J* = 7.5 Hz, 4H), 5.14 (ddd, *J* = 30.1, 19.8, 3.6 Hz, 2H), 4.77 (t, *J* = 6.5 Hz, 1H), 4.67 (dd, *J* = 52.8, 12.0 Hz, 1H), 4.22 – 4.19 (m, 2H), 4.13 – 4.07 (m, 1H), 4.03 (d, *J* = 12.1 Hz, 1H), 3.90 – 3.86 (m, 2H), 3.84 (s, 2H), 3.81 (d, *J* = 2.7 Hz, 1H), 3.78 (s, 3H), 3.67 (dd, *J* = 14.6, 2.5 Hz, 0.5H), 3.61 (s, 3H), 2.91 (s, 0.6H), 2.73 (d, *J* = 10.3 Hz, 1H), 2.46 (dd, *J* = 22.3, 7.4 Hz, 2H), 2.39 – 2.36 (m, 2H), 2.34 (s, 3H), 2.33 (s, 3H), 2.29 – 2.25 (m, 2H), 2.19 (d, *J* = 13.0 Hz, 1H), 2.14 – 2.09 (m, 2H), 1.78 (dd, *J* = 13.9, 3.2 Hz, 1H), 1.48 (dd, *J* = 14.0, 6.4 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 174.6, 174.1, 170.8, 170.6, 144.2, 141.9, 141.3, 139.9, 139.2, 138.8, 137.7, 137.6, 137.3, 129.3, 128.8, 128.7, 128.1, 127.9, 126.3, 126.2, 126.0, 125.9, 98.9, 96.1, 77.8, 76.6, 74.2, 70.8, 70.6, 69.5, 69.0, 57.8, 53.2, 52.9, 52.8, 52.6, 50.6, 48.8, 37.2, 36.3, 35.1, 34.7, 34.0, 32.6, 32.2, 31.8, 30.2, 21.3; For compound **6, HRMS (+APCI):** Calcd for $C_{23}H_{25}O_4$ $[M\text{-}OH]^+$ 365.1753; found: 365.1754; For compound **5, HRMS (+APCI):** Calc for $C_{24}H_{27}O_5$ $[M\text{-}OH]^+$ 395.1859; found: 395.1857.

^{1}H NMR of compound 6 after recrystallization

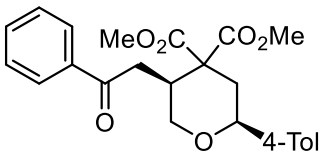


6

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.40 – 7.34 (m, *J* = 15.1, 7.3 Hz, 4H), 7.30 (t, *J* = 7.0 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 7.9 Hz, 2H), 5.18 (dd, *J* = 12.4, 2.6 Hz, 1H), 5.15 (d, *J* = 3.2 Hz, 1H), 4.21 (d, *J* = 9.8 Hz, 1H), 4.09 (dd, *J* = 12.0, 2.5 Hz, 1H), 3.85 (s, 3H),

3.80 (d, *J* = 12.0 Hz, 1H), 2.72 (dd, *J* = 13.9, 9.0 Hz, 2H), 2.34 (s, 3H), 2.32 – 2.25 (m, 2H), 2.19 (t, *J* = 11.4 Hz, 1H).

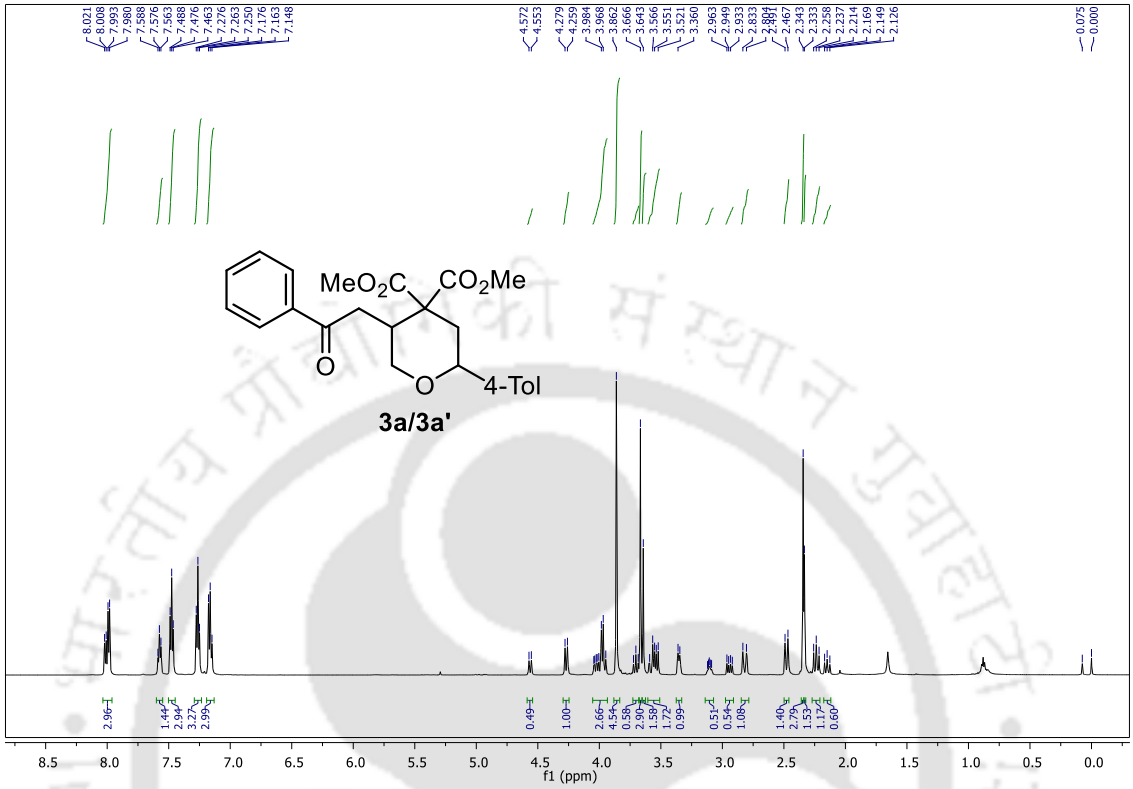
^{1}H and ^{13}C NMR data for single diastereomer of compound 3a

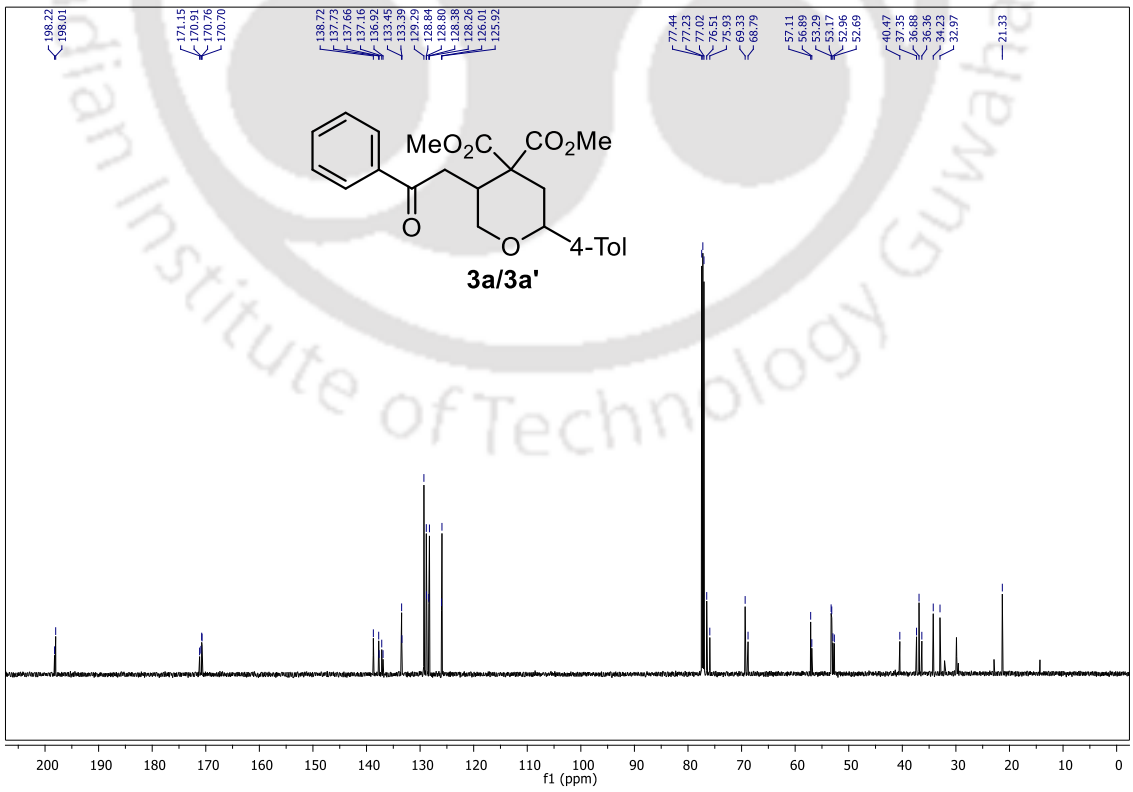


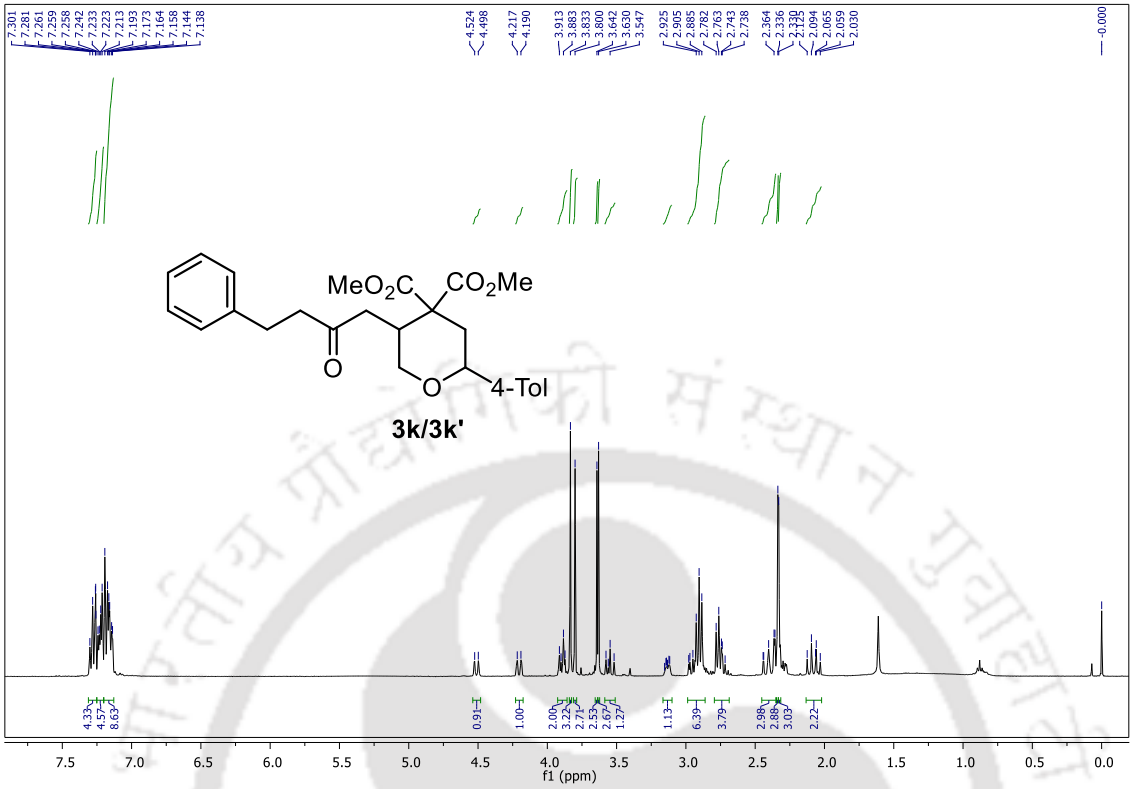
3a

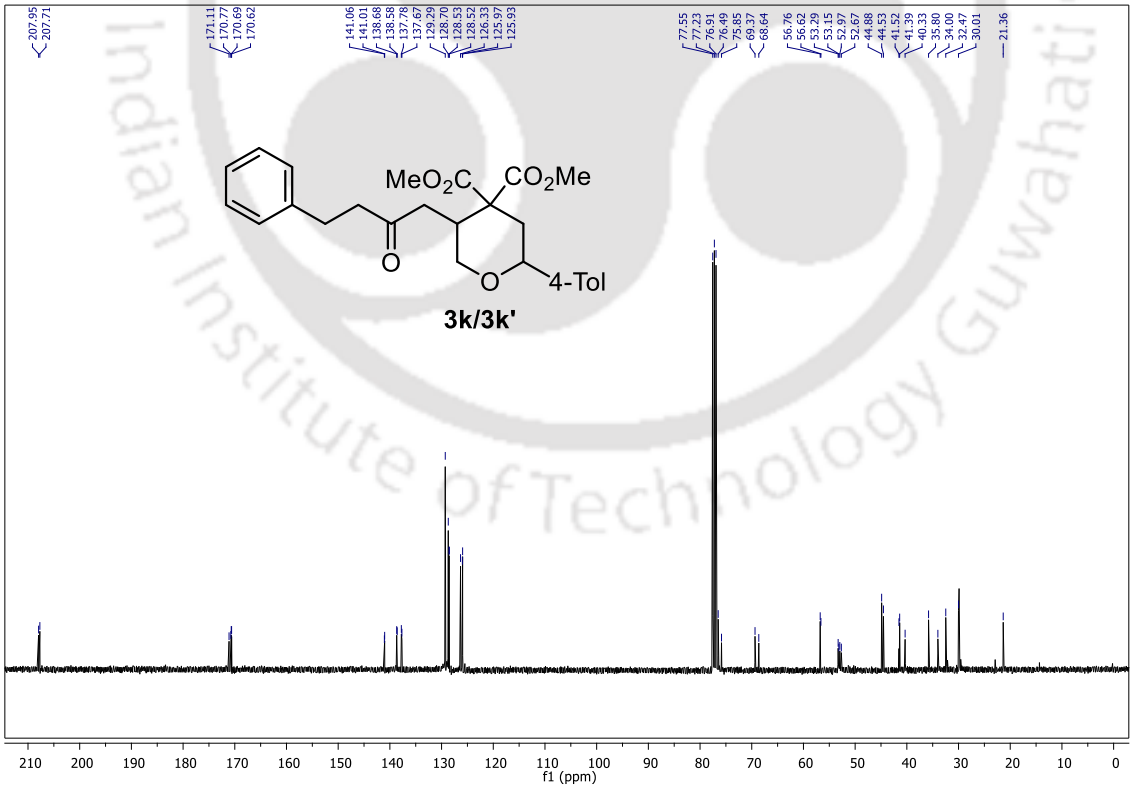
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.99 (d, *J* = 7.5 Hz, 2H), 7.58 (t, *J* = 7.3 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 2H), 7.27 (d, *J* = 8.1 Hz, 2H), 7.17 (d, *J* = 7.8 Hz, 2H), 4.27 (d, *J* = 11.3 Hz, 1H), 3.98 (q, *J* = 12.3 Hz, 2H), 3.86 (s, 3H), 3.67 (s, 3H), 3.55 (dd, *J* = 17.6, 9.4 Hz, 1H), 3.35 (d, *J* = 8.4 Hz, 1H), 2.81 (d, *J* = 17.6 Hz, 1H), 2.48 (d, *J* = 14.3 Hz, 1H), 2.35 (s, 3H), 2.24 (t, 1H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 198.0, 170.8, 170.7, 138.7, 137.7, 137.2, 133.5, 129.3, 128.8, 128.3, 125.9, 76.5, 69.3, 57.1, 53.3, 53.2, 36.9, 34.2, 32.9, 21.3.

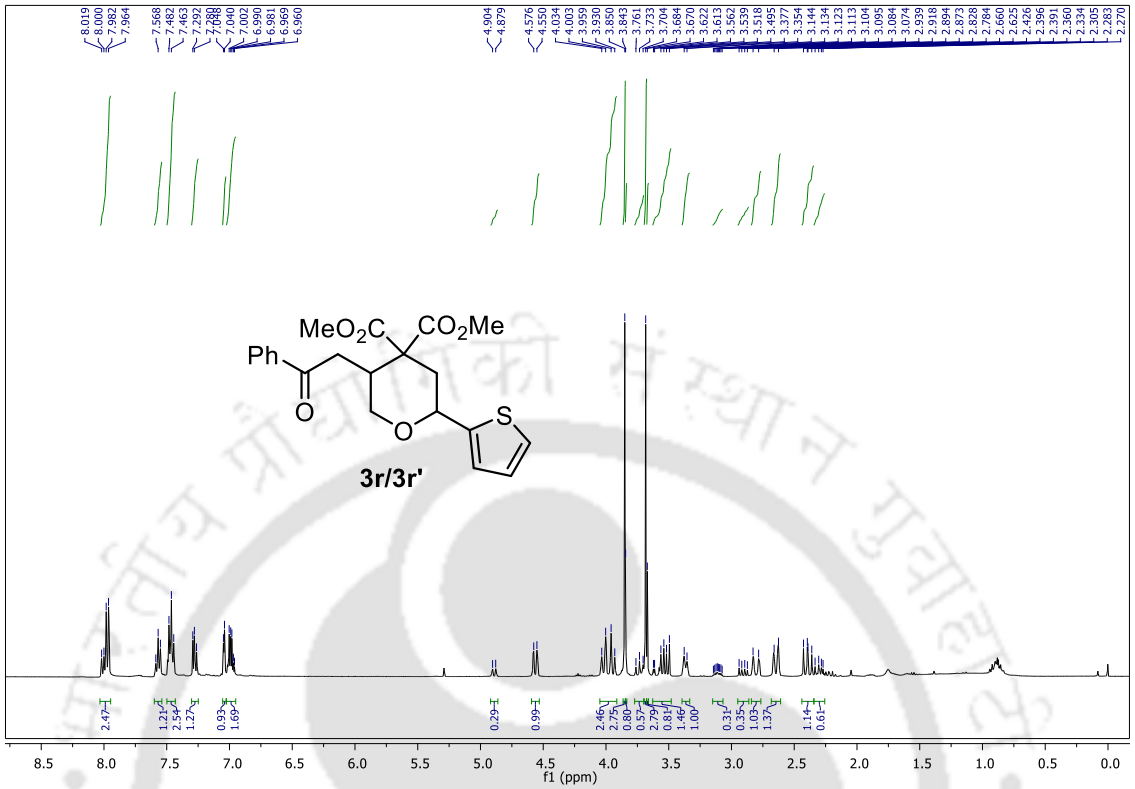
3.9 Selected spectra of products

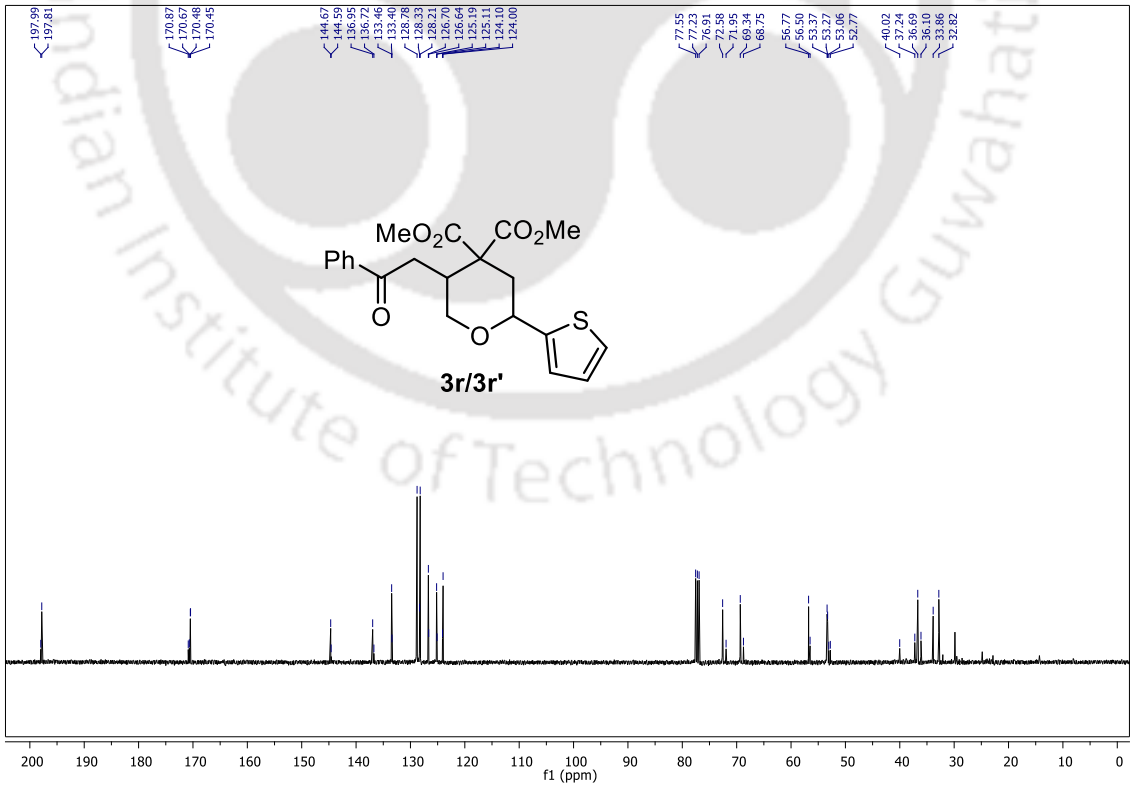




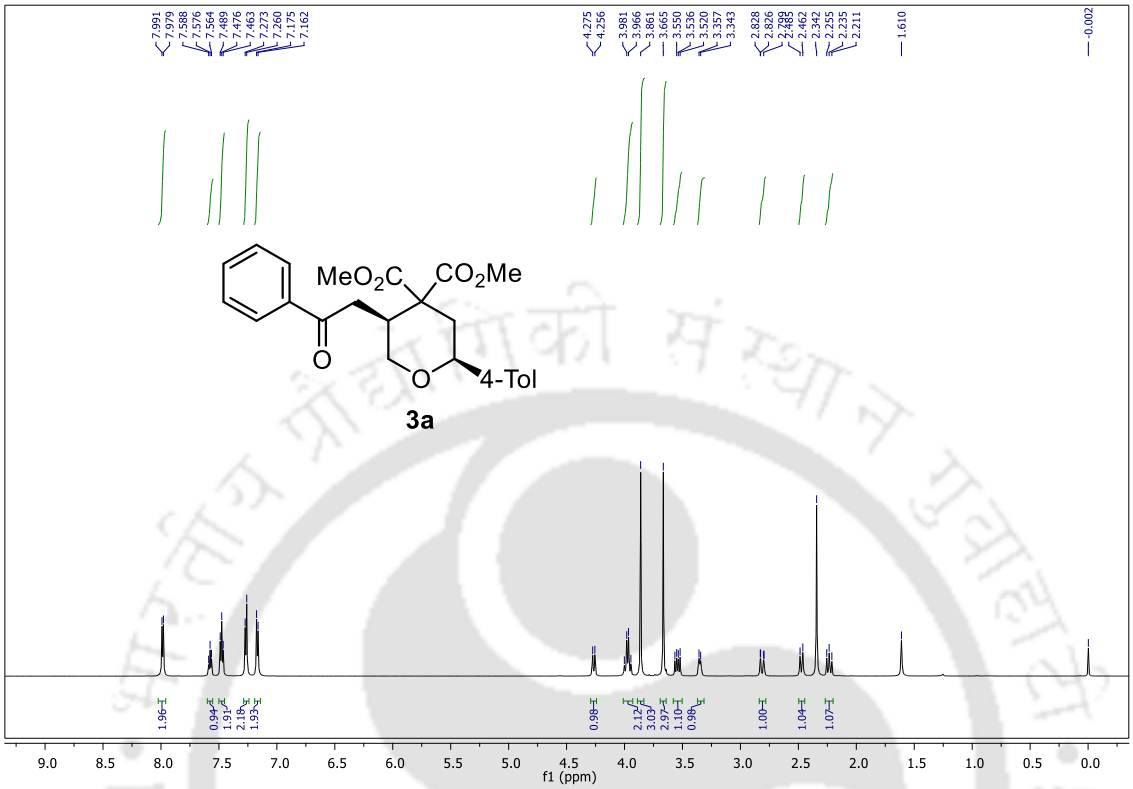


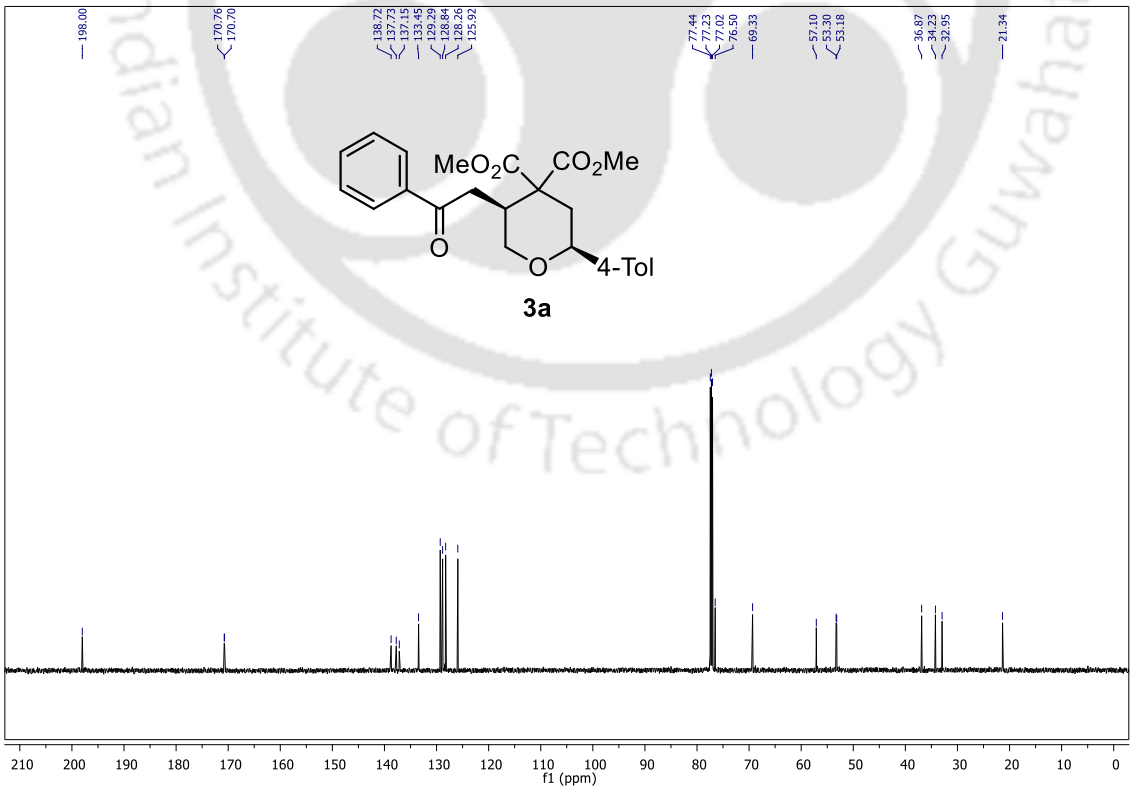




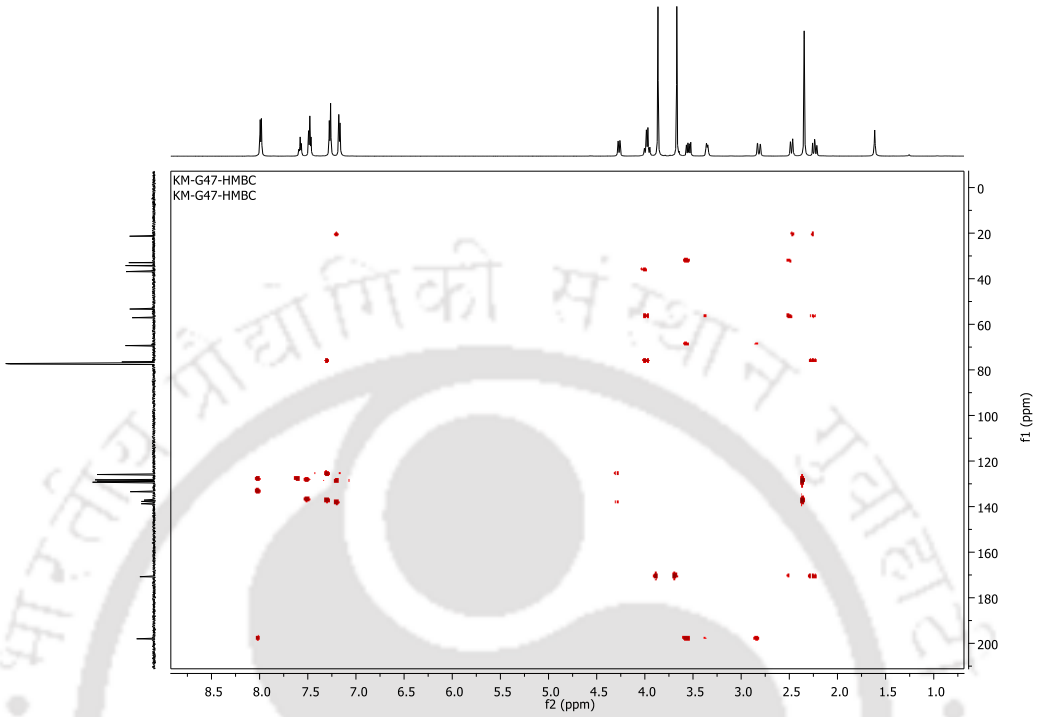


Spectra of single diastereomer compound 3a

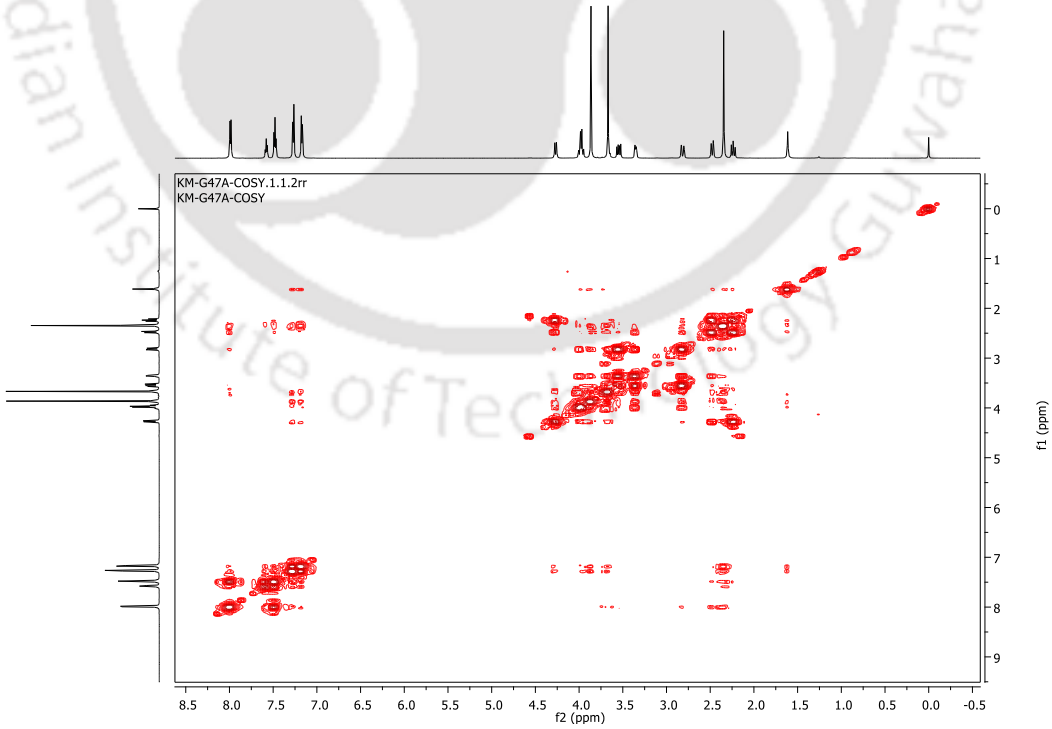




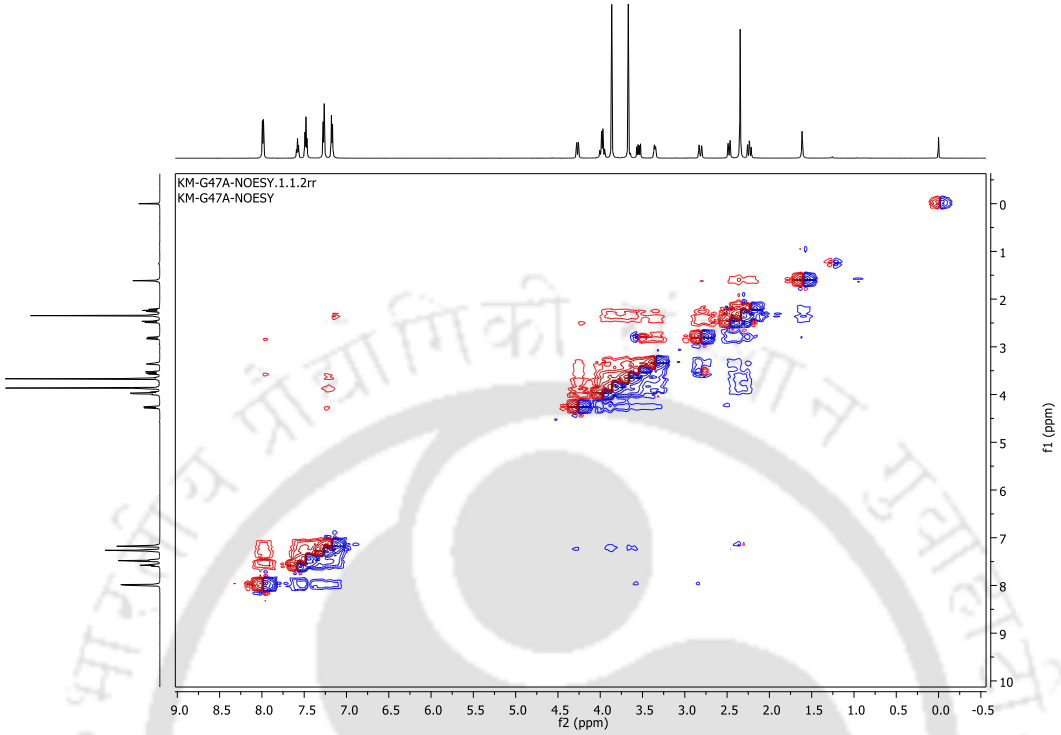
HMBC spectra of compound 3a

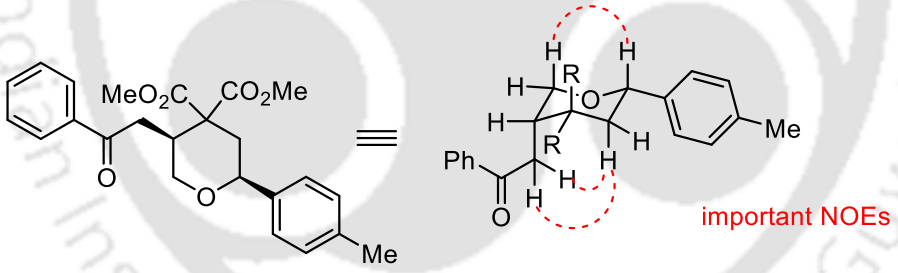


COSY spectra of compound 3a



NOESY spectra of compound 3a





Chapter 4

Synthesis of 2,5-Disubstituted Furans from $Sc(OTf)_3$ Catalyzed Reaction of Aryl Oxiranediesters with γ-Hydroxyenones

4.1 Introduction

2,5-Disubstituted furans are important five-membered heterocyclic compounds present in a wide range of biologically active natural products and pharmaceuticals and some of the representative examples have been shown in Figure 4.1.[1] Also, this moiety was utilized as a versatile building block in organic synthesis.[2] For this reason, significant attention has been paid by the synthetic chemists for the construction of substituted furans.[3]

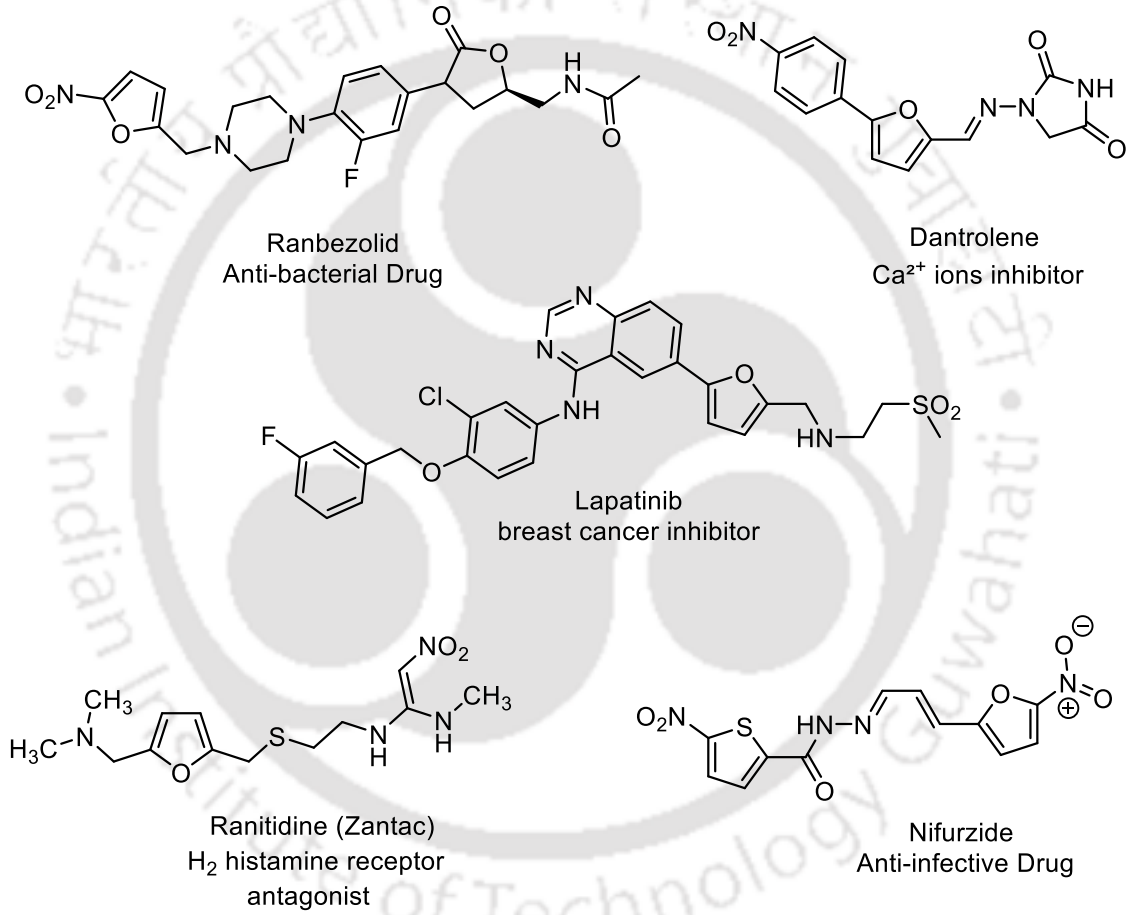


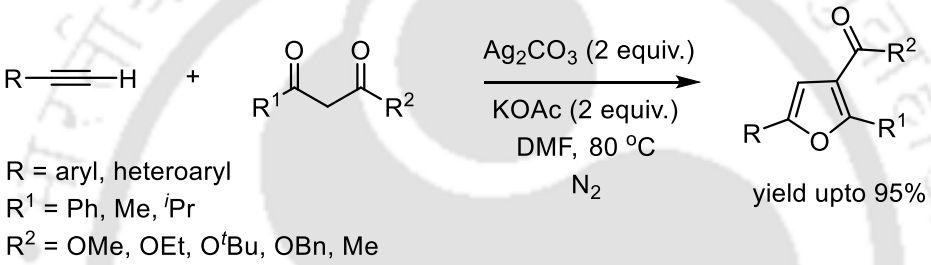
Figure 4.1: Furan derived biologically active natural products

However, one of the continuing challenges is the diverse access to 2,5-disubstituted furans with different functionalities. The main approaches to 2,5-disubstituted furans involve the functionalization of pre-existing furan precursors[4] and metal catalyzed cyclization reactions of unsaturated alcohols, unsaturated ketones, and haloalkynes or 1,3-diynes with ketones or aldehydes.[5]

4.2 Synthesis of substituted furan derivatives

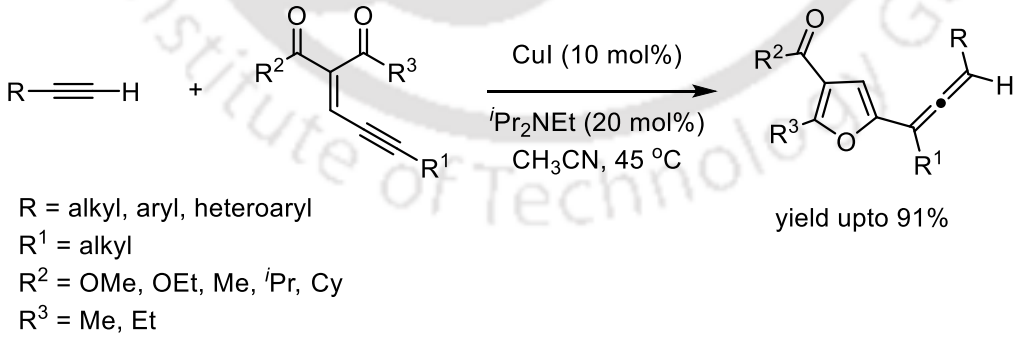
Over the past few decades, different approaches have been developed for the synthesis of substituted furans.[6] In general, Feist-Bénary condensation and Paal-Knorr condensation are one of the traditional and well-established methods to construct the substituted furans. Here, few reported methods have been discussed for the synthesis of substituted furan compounds.

Lei *et al*. reported a simple and atom-economic protocol to construct highly substituted furans *via* C–H functionalization of 1,3-dicarbonyl with terminal alkyne in the presence of silver carbonate with good to excellent yields (Scheme 4.1).[7]



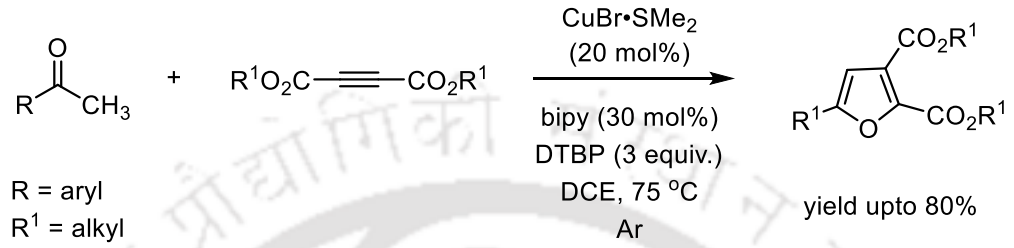
Scheme 4.1: Ag_2CO_3 mediated synthesis of substituted furans

A new strategy for the synthesis of substituted furan allene derivatives was demonstrated by Wang and his co-workers. This group has reported the coupling reaction between ene-yne ketone and terminal alkyne using Cu(I)-catalyst (Scheme 4.2).[8]



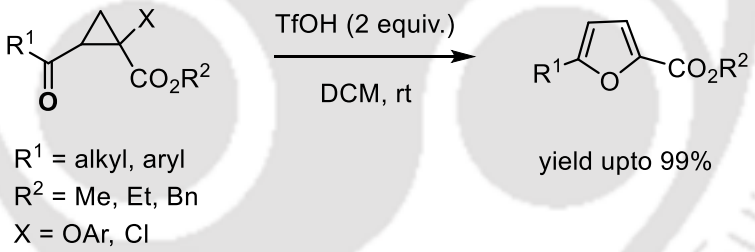
Scheme 4.2: CuI catalyzed synthesis of substituted furan allenes

Antonchick group developed an efficient method to construct multisubstituted furans from readily available starting material acetophenones and activated alkynes under the catalysis of Cu(I)-salt; and di-*tert*-butyl peroxide was used as an external oxidant. It was observed that the reaction proceeded *via* the radical pathway (Scheme 4.3).[9]



Scheme 4.3: Synthesis of multisubstituted furans

Gong *et al*. achieved a direct synthetic route for the synthesis of 2,5-disubstituted furans from donor-acceptor cyclopropanes *via* ring opening reaction followed by cycloisomerization reaction in the presence of triflic acid with good yields. The reaction was highly dependent on the properties of acid employed in the reaction (Scheme 4.4).[10]



Scheme 4.4: Synthesis of 2,5-disubstituted furans

4.3 Reaction with donor-acceptor oxiranes

In recent years, donor-acceptor oxiranes have emerged as an important synthetic building blocks due to their ease of preparation and their tendency for strain-induced ring opening reactions.[11] The common reactions of donor-acceptor oxiranes involve either C−O bond cleavage or C−C bond cleavage shown in Figure 4.2, and the overall process is usually controlled by the choice of Lewis and Brønsted acid.

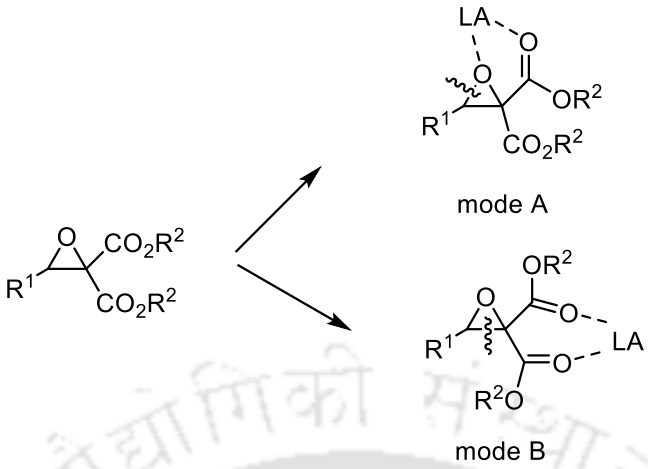
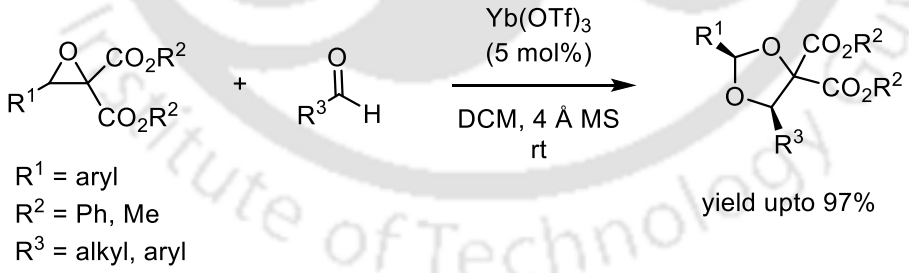


Figure 4.2. Proposed routes for the oxirane bond cleavage reactions (mode A: C−O bond cleavage and mode B: C−C bond cleavage)

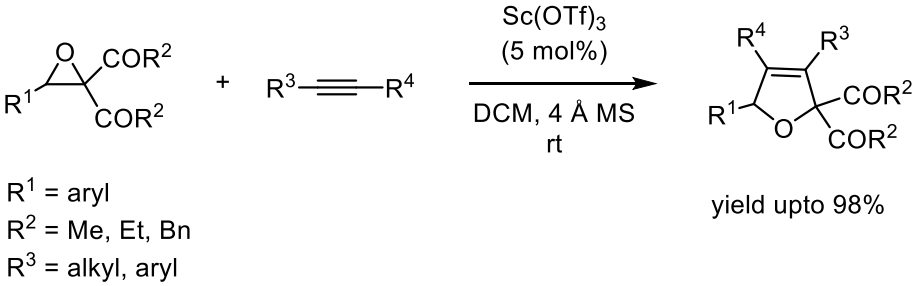
These two modes resulted in two different ring opening pathways of the epoxide motif which could react with various dipolarophiles to construct different oxygenated heterocyclic compounds. A variety of strategies have been developed utilizing DA-oxiranes in organic synthesis.

For example, Zhang group reported highly diastereoselective Lewis acid catalyzed reaction of 1,3-dipolar oxiranes and aldehydes for the synthesis of *cis*-2,5-disubstituted 1,3-dioxolanes at ambient temperature with excellent yields (Scheme 4.5).[12]



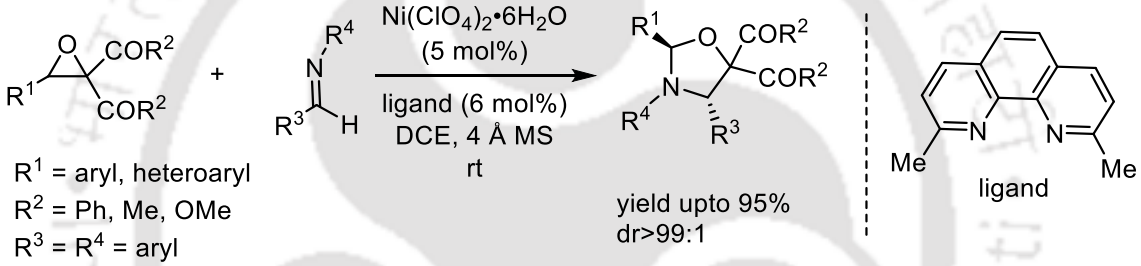
Scheme 4.5: Synthesis of substituted 1,3-dioxolanes

In 2011, the same research group investigated scandium(III)triflate catalyzed highly regioselective formal [3 + 2] cycloaddition reaction of DA-oxiranes and alkynes under mild reaction conditions. The reaction proceeded *via* C−C bond cleavage of epoxide for the construction of substituted dihydrofurans (Scheme 4.6).[13]



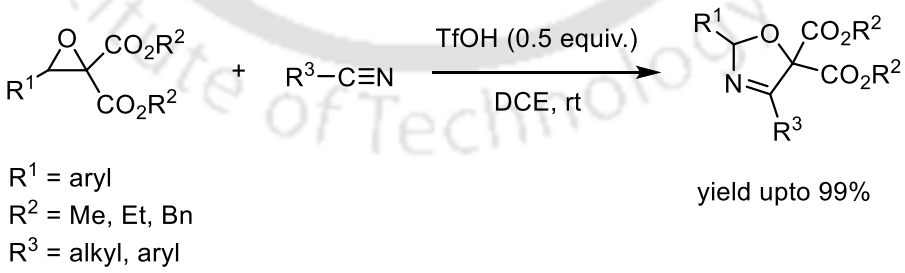
Scheme 4.6: Synthesis of substituted dihydrofurans

Further, an efficient method to synthesize highly substituted 2,4-*trans* oxazolidines *via* [3 + 2] cycloaddition reaction of DA-oxiranes and imines was developed by Zhang and co-workers using Ni(II)-catalyst with high diastereoselectivity (Scheme 4.7).[14]



Scheme 4.7: Synthesis of 2,4-oxazolidine derivatives

Recently, Zhong *et al*. published formal [3 + 2] cycloaddition reaction between DA-oxiranes and nitrile in the presence of triflic acid for the synthesis of 3-oxazoline derivatives (Scheme 4.8).[15]



Scheme 4.8: Synthesis of 3-oxazoline derivatives

4.4 Result and discussion

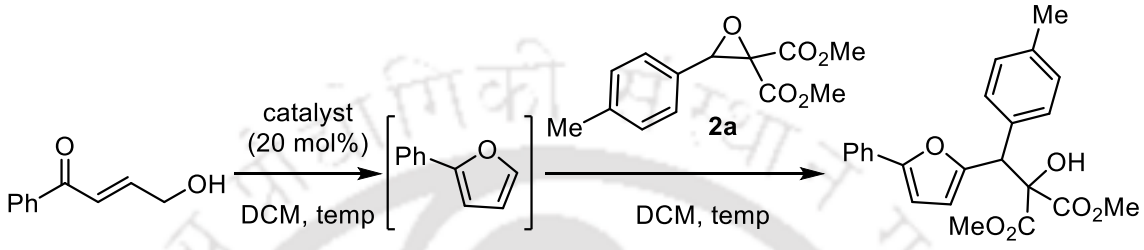
From the literature report, it was found that donor-acceptor cyclopropanes have previously been exploited in the synthesis of multisubstituted[3b-c] and 2,5-disubstituted furans,[10] but donor-acceptor oxiranes were unexplored in the synthesis of furans. Previous traditional methods suffer from some disadvantages such as substrate scope limitation, harsh reaction conditions and longer reaction times. Therefore, it is still a requirement for the development of new and efficient strategies using easily accessible starting materials for the synthesis of disubstituted furans. During the course of our investigation on developing cycloaddition reactions with *γ*-hydroxyenones,[16] it was envisaged that donor-acceptor oxiranes might undergo similar cycloaddition reactions. But herein, we have revealed an unexpected formation of 2,5-disubstituted furans employing donor-acceptor oxiranes and *γ*-hydroxyenones.

To attain the sustainable reaction condition, a model reaction was performed between 3-benzoyl prop-2-en-1-ol (**1a**) and dimethyl 3-*p*-tolyloxirane-2,2-dicarboxylate (**2a**) in DCM at 35 °C (Table 1). Using $Sc(OTf)_3$ as a catalyst, after 1.5 h, a product was isolated in 29% yield. The product was identified as dimethyl 2-hydroxy-2-((5-phenylfuran-2-yl)(ptolyl)methyl)malonate (**3a**) by ^1H and ^{13}C NMR analysis as well as by X-ray crystal structure[17]. After this initial success, to obtain better result, other parameters such as catalyst, solvent, and temperature were screened. Unfortunately, satisfactory results were not attained. Interestingly, the yield was enhanced to 49% when **1a** was stirred with $Sc(OTf)_3$ for 45 min before addition of **2a** and subsequent stirring for another 1 h (Table 1, entry 1). This was due to the initial formation of 2-phenylfuran (**A**), which later reacts with oxiranediester **2a**. Thus, the next experiments of catalyst screening were carried out under this condition. A similar yield of **3a** was attained using TMSOTf as a catalyst under this condition (Table 1, entry 2). A strong Brønsted acid such as triflic acid also provided the moderate yield of the furan product **3a** (Table 1, entry 3). However, only trace amounts of the product **3a** were detected using ytterbium trifluoromethanesulfonate, ferric chloride, cerium chloride, and *p*-toluene sulfonic acid as catalysts (Table 1, entries 4-7). Other catalysts such as copper

trifluoromethanesulfonate and stannous trifluoromethanesulfonate were also screened and were found to be less efficient for this reaction (Table 1, entries 8-9).

Optimization of reaction condition

Table 1: Catalyst screening



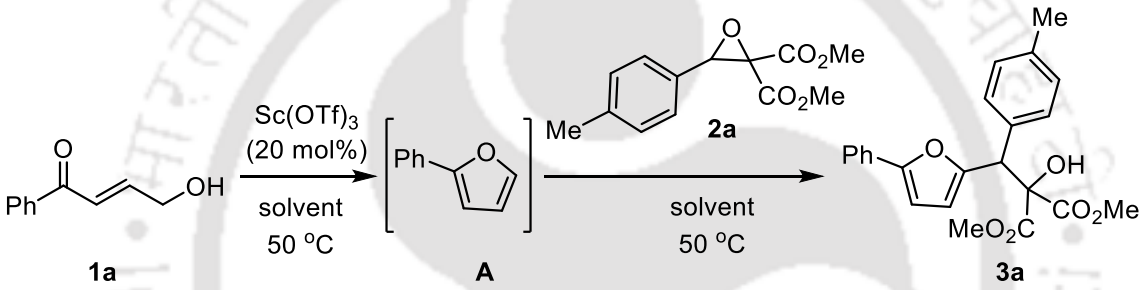
1a **A** **3a**

entry[a]	catalyst	temp (°C)	time (min)	yield (%)[b]
1	$Sc(OTf)_3$	35	105	49
2	TMSOTf	35	105	46
3	TfOH	35	105	40
4	$Yb(OTf)_3$	35	105	<5
5	$FeCl_3$	35	105	<5
6	$CeCl_3•7H_2O$	35	105	<5
7	PTSA	35	105	<5
8	$Cu(OTf)_2$	35	105	10
9	$Sn(OTf)_2$	35	105	25
10	$BF_3•OEt_2$	35	105	Mixture of product
11	$Sc(OTf)_3$	50	60	53
12[c]	$Sc(OTf)_3$	50	60	68
13[d]	$Sc(OTf)_3$	50	16	55

[a]Reaction conditions: Unless otherwise mentioned 0.1 mmol of **1a** and 0.15 mmol of **2a** in 0.5 mL DCM using 20 mol% catalyst at 35-50 °C. [b]Isolated yield after silica gel column chromatography. [c]With 0.2 mmol of **2a**. [d]With 10 mol% of catalyst.

In case of boron trifluoride etherate, a mixture of products was observed under the reaction condition (Table 1, entry 10). Thus, the reaction was carried out with $Sc(OTf)_3$ for further optimization. Pleasingly, enhancement in yield was observed by performing the reaction at 50 °C, and the reaction time was also shortened (Table 1, entry 11). Finally, the best yield (68%) was achieved by using **2** equiv. of **1a** (Table 1, entry 12). Lowering the amount of catalyst (10 mol%) decreased the yield of furan product. Next, the effect of other solvents was also examined under similar reaction conditions but only poor results were obtained (Table 2). Toluene and 1,2-dichloromethane provided the products with moderate yields 33% and 49% respectively (Table 2, entries 2-3).

Table 2: Solvent screening



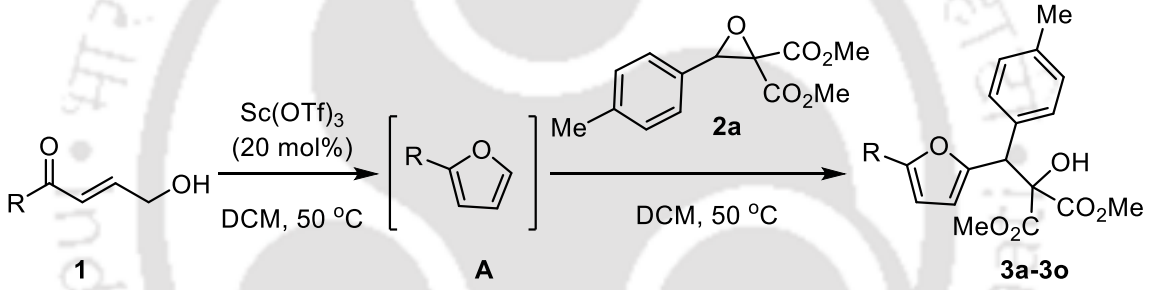
entry[a]	solvent	time (min)	yield (%)[b]
1	DCM	60	68
2	$PhCH_3$	60	33
3	DCE	60	49
4	CH_3CN	60	<5
5	THF	60	<5

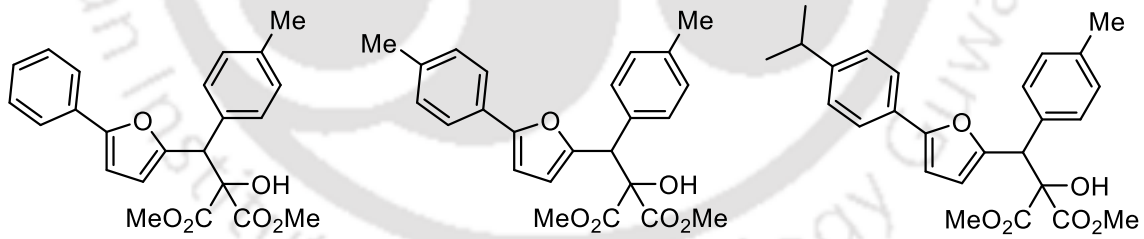
[a]Reaction conditions: Unless otherwise mentioned 0.1 mmol of **1a** and 0.15 mmol of **2a** in 0.5 mL DCM using 20 mol% catalyst at 50 °C. [b]Isolated yield after silica gel column chromatography.

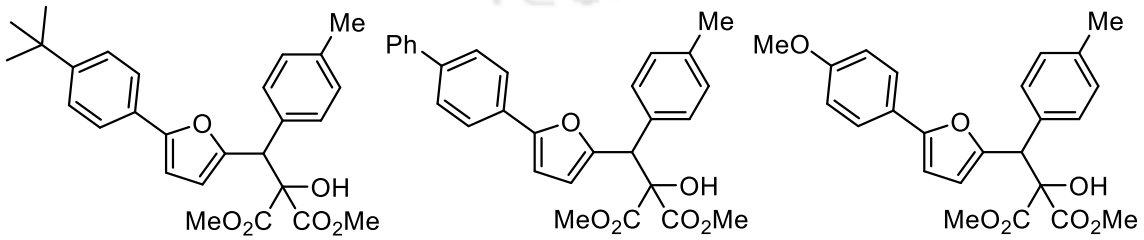
Polar solvents such as acetonitrile and tetrahydrofuran were also not suitable for this reaction and a trace amounts of product were detected (Table 2, entries 4-5). The reaction was also carried out at higher temperature in DCE solvent, but lower yield was observed.

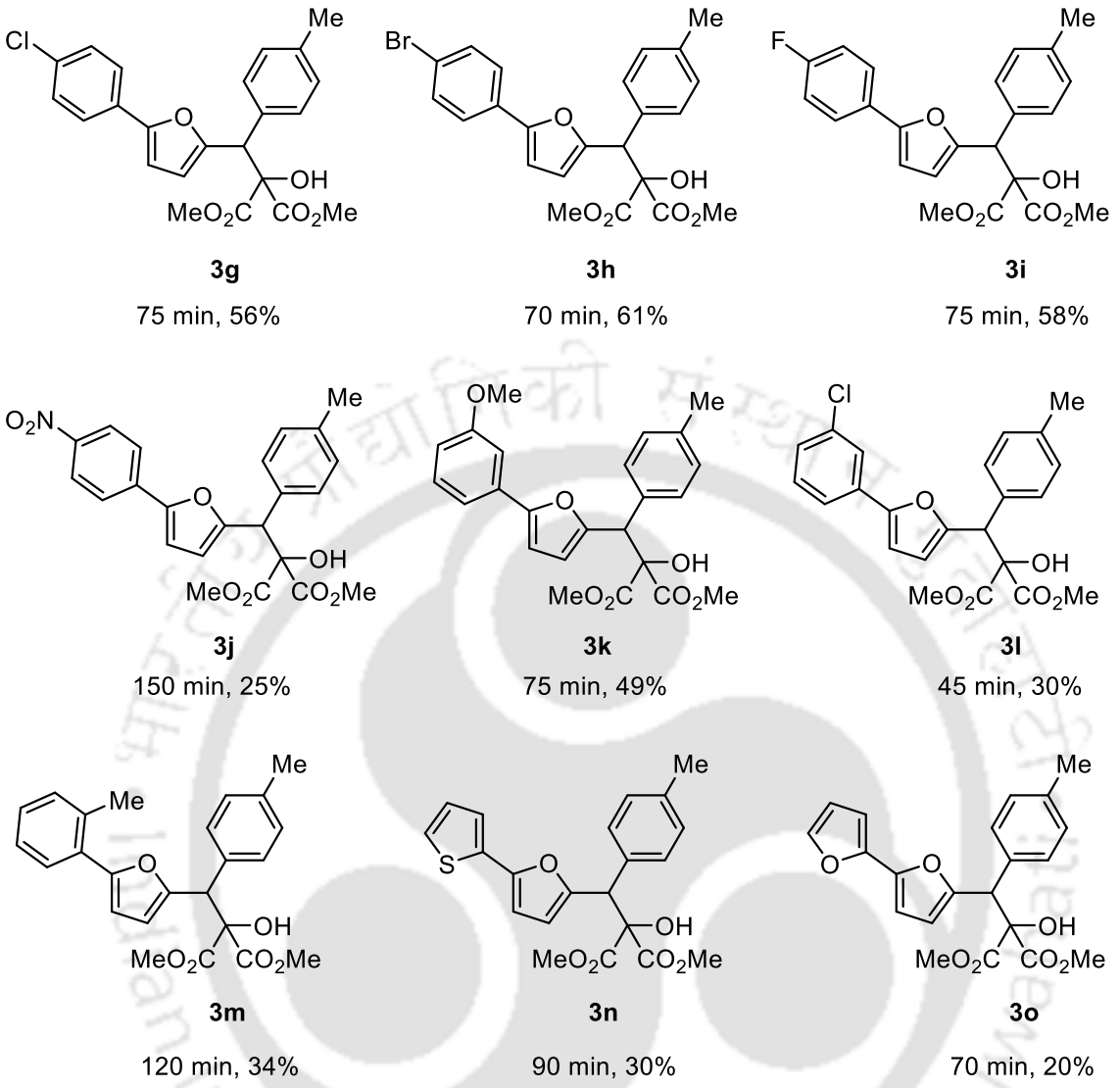
4.5 Substrate scope

After the optimized conditions were identified, the generality and scope of the reaction was investigated. First, *p*-tolyl oxiranediester **2a** was fixed as substrate and then a variety of γ-hydroxyenones **1** were screened under this reaction conditions (Scheme 4.9). Gratifyingly, different electron-neutral, electron-withdrawing, and electron-donating groups were tolerated at the *ortho*, *meta*, and *para* position of the aryl ring. At first, enones **1b**-**1d** having different alkyl groups at the *p*-positions of the phenyl ring were screened, and good results were attained. For example, enones having 4-methyl **1b** and 4-*iso*-propyl **1c** substituents in the aryl ring delivered the corresponding products **3b** and **3c** in 51% and 64% yields respectively. 4-*tert*-Butyl enone **1d** furnished the product **3d** and the result was found to be similar with 4-methyl substituted compound **3b**.









[a]Reaction conditions: All reactions were carried out with 20 mol% of $Sc(OTf)_3$ in DCM at 50 °C using 0.1 mmol of **1** and 0.2 mmol of **2a**. [b]Isolated yield after silica gel column chromatography.

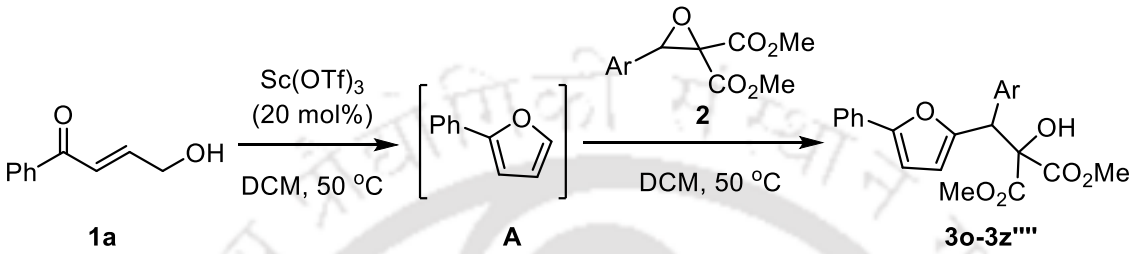
Scheme 4.9: Scope of furan with different γ-hydroxyenones[a,b]

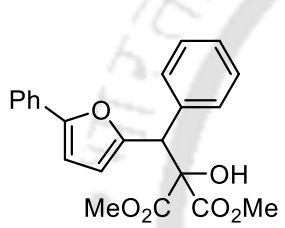
Enone **1e** having biphenyl motif also provided the corresponding product **3e** in a good yield of 59%. Decent yield (66%) was achieved with enone **1f** having a 4-anisyl group. It was found that different 4-halo substituted aryl groups containing enones **1g-Ii** were served as good substrate for this reaction and the products were isolated in acceptable yields. Products **3g** and **3i** were obtained in comparable yields of 56% and 58% respectively, but slight better yield (61%) was observed for 4-bromo substituted enone.

Electron-poor enone **1j** having a nitro group also took part in the reaction; however, the yield was less (25%). Next, different *m*-substitutions were explored, and it was found that electron-donating groups at the *m*-positions were better than electron-withdrawing groups. The monosubstituted furan **A** was formed smoothly from different γ-hydroxyenones under this condition, but Friedel–Crafts reaction followed by ring opening of oxiranes was slow for electron-withdrawing groups compared to the electron-donating groups present in the aryl ring. Enones **1k** and **1l** having 3-methoxy and 3-chloro substituents respectively resulted the furan products **3k** and **3l** in 49% and 30% yield correspondingly. This methodology was also applicable to *o*-substituted aryl group containing enone **1m** despite less yield (34%) was obtained. Finally, heteroaromatic enones **1n** and **1o** were screened in the reaction and moderate yields were observed for products **3n** and **3o**.

The next phase of experiments involved incorporation of a range of oxiranediesters **2** (Scheme 4.10). Here, a variety of substitutions on the aryl ring was also compatible for the reaction. Though, phenyl group containing oxiranediaster **2b** provided moderate yield (37%) of the product **3p**. But interestingly, higher yields were achieved with electron-neutral or electron-donating *p*-substituted aryl group containing oxiranediesters. For example, oxirane **2c** having a 4-*iso*-propylphenyl group provided the product **3q** in 62% yield in a quick reaction time. The reaction proceeded well with oxirane **2d** having 4-*tert*-butyl group with 50% isolated yield. Gratifyingly, oxirane **2e** having a biphenyl motif delivered the product **3s** in a higher yield of 73%. Furthermore, different 4-alkoxy substituted aryl groups containing oxiranes were screened and delightfully, the outcomes were satisfactory, and around 70-80% yields were attained in all cases. The highest yield of 78% was achieved with oxirane **2f** having a 4-anisyl group. The other 4-alkoxy group such as 4-ethoxy (**2g**), 4-*n*-propyloxy (**2h**) and 4-*iso*-propyloxy (**2i**) containing oxiranes provided the corresponding products **3u-w** with 77%, 74%, and 75% yields respectively. However, 4-halosubstituted oxiranes also participated in the reaction and the products **3x-z** were isolated in moderate yields. 4-fluoro and 4-chloro containing oxiranes **2j** and **2k** underwent reaction with **1a** to afford furan products **3x** and **3y** in 35% and 36% isolated yields. For 4-bromo oxirane, the yield of **3z** was similar to **3y**.

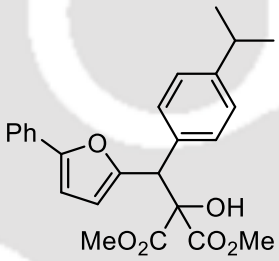
From these investigations, it was revealed that 4-electron-donating substituents accomplished superior results compared to the 4-electron-withdrawing substituents in the aryl ring. This has happened due to the lack of carbocation stability that is formed during the ring opening of oxiranediesters and is responsible for the formation of desired furan products.





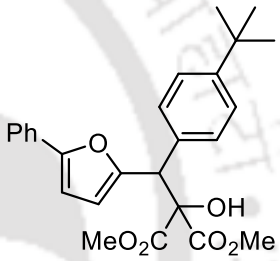
3p

85 min, 37%



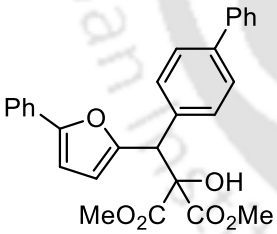
3q

60 min, 62%



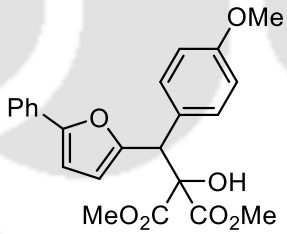
3r

60 min, 50%



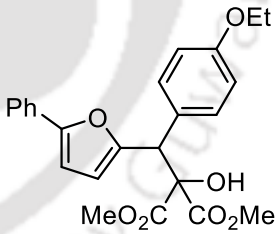
3s

60 min, 73%



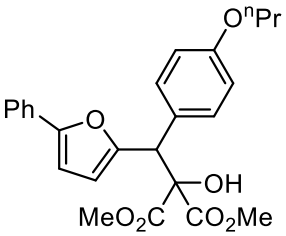
3t

60 min, 78%



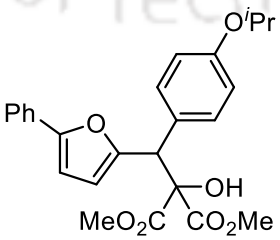
3u

60 min, 77%



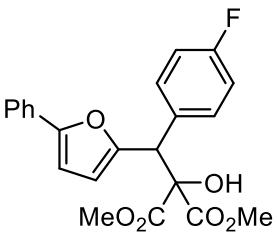
3v

60 min, 74%



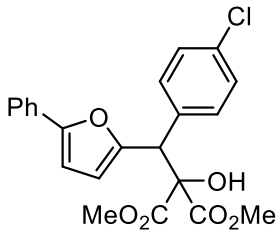
3w

60 min, 75%



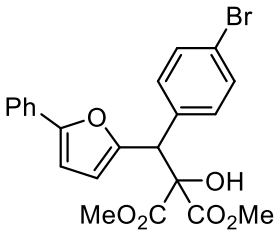
3x

80 min, 35%



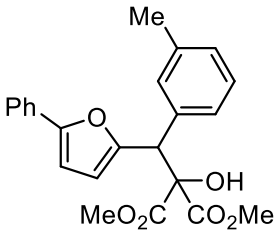
3y

70 min, 36%



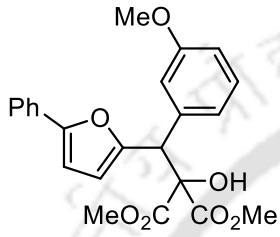
3z

75 min, 36%



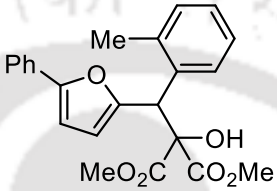
3z'

90 min, 40%



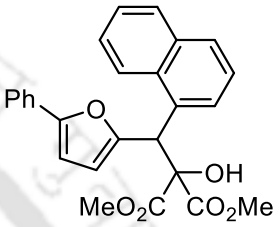
3z''

70 min, 56%



3z'''

65 min, 40%



3z''''

70 min, 65%

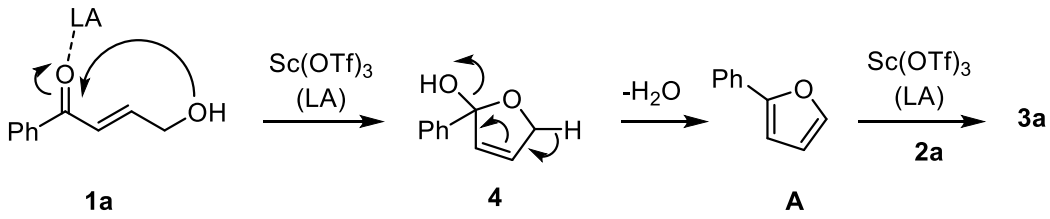
[a]Reaction conditions: All reactions were carried out with 20 mol% of $Sc(OTf)_3$ in DCM at 50 °C using 0.1 mmol of **1a** and 0.2 mmol of **2**. [b]Isolated yield after silica gel column chromatography.

Scheme 4.10: Scope of furan with different oxirane-1,1-diesters[a,b]

The substitutions at the *ortho* and *meta* positions were also well tolerated and the good results were attained. The corresponding product (**3z′**) was obtained with a moderate yield of 40% by using 3-methyl substituted oxirane (**2m**), but better yield (56%) was observed for the product **3z′′** with 3-methoxy containing oxirane (**2n**). In addition, oxirane **2o** having 2-methyl group was also incorporated under the reaction, delivering the product **3z′′′** in 40% yield. Finally, a 1-naphthyl group containing oxirane **2p** was engaged in the reaction, and a decent yield of 65% was attained for the product **3z′′′′**.

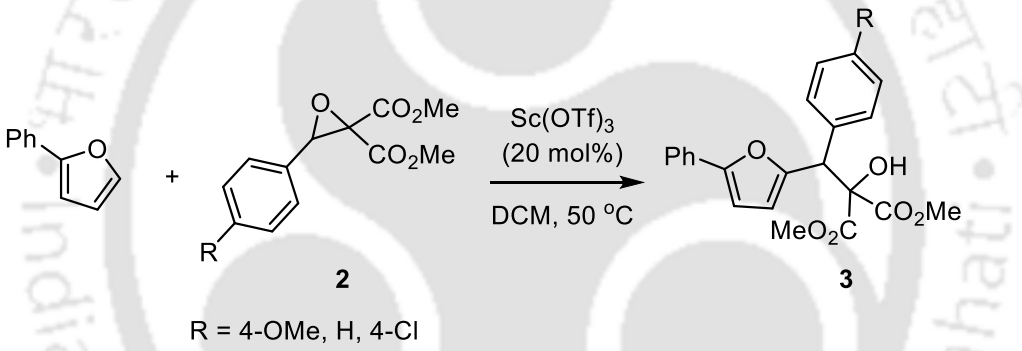
On the basis of literature survey, a plausible mechanism for the formation of furan **3a** has been shown in Scheme 4.11. At first, $Sc(OTf)_3$ activates the carbonyl group of **1a** for an intramolecular nucleophilic attack by the hydroxyl group and thus, **4** is generated with a *Z*-configured double bond for geometric reasons.[18] After elimination of water, 2-phenylfuran (**A**) is formed, which has been confirmed by ^1H and ^{13}C NMR studies. Then,

the Friedel–Crafts reaction between **A** and oxiranediester **2a** followed by ring opening of oxirane (**2a**) was catalyzed by $Sc(OTf)_3$ to provide the desired disubstituted furan **3a**.



Scheme 4.11. Proposed mechanism for the formation of furan

The Hammett study was then performed in different donor-acceptor oxiranes having *p*-substitution in the aryl group to understand the electronic substituent effect on the reaction (Scheme 4.12). After formation of 2-phenylfuran (**A**), oxirane **2** was added, and then the rate of the conversions was studied by ^{1}H NMR shown in Figure 4.3.



Scheme 4.12: Hammett analysis

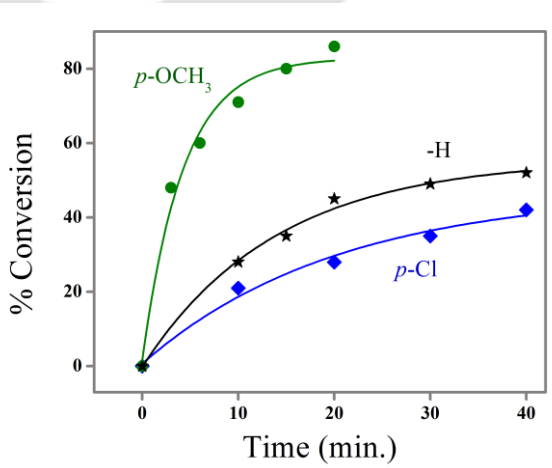


Figure 4.3: Time *vs* %Conversion for different *p*-substituent oxiranes

After that, the order of the reaction was determined and it was found to be 1st order with respect to ln[4-OMe oxiranes] represented in Figure 4.4. Finally, log(K_X/K_H) *vs* σ_p (substituent constant) has been plotted (Figure 4.5) and the value of the rate constant has been determined which was given in Table 3. Also, the data has been provided for σ_p (substituent constant) of different *p*-substituted oxiranes from the literature.

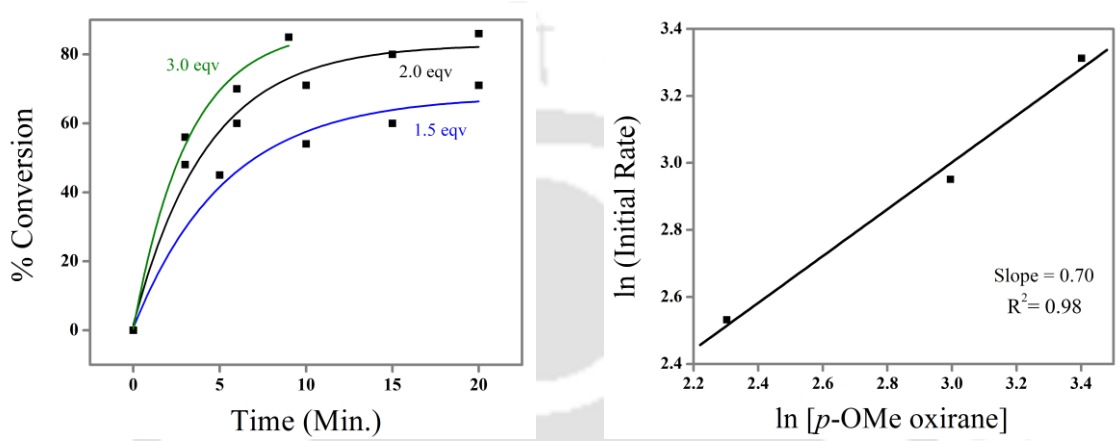


Figure 4.4: Time *vs* %Conversion for *p*-OMe-substituted oxiranes using different equivalent (**left**) and ln(Initial Rate) *vs* ln[*p*-OMe oxirane], to determine the rate of the reaction (**right**)

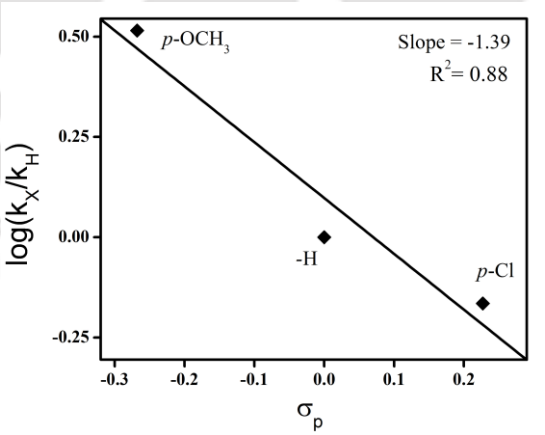


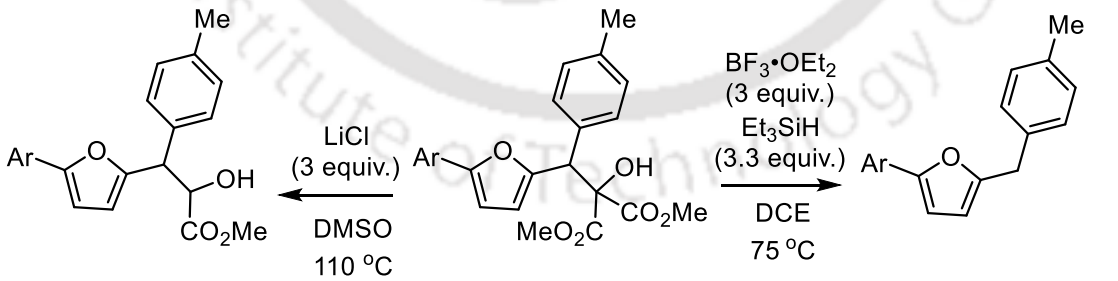
Figure 4.5: log(K_X/K_H) *vs* σ_p (substituent constant)

Table 3: Determination of the rate constant for different *p*-substituted oxiranes and literature provided the σ_p (substituent constant)

entry	R	K_X (rate constant)	$\log(K_X/K_H)$	σ_p (substituent constant)
1	*p*-OCH_3	0.2353/min	0.5155	-0.268
2	H	0.0717/min	0	0
3	*p*-Cl	0.0491/min	-0.1650	0.227

From this graph (Figure 4.5), the negative reaction constant value (slope = −1.39) was observed which indicates that the larger the electron dispersion from the benzylic carbon of oxiranes, slower the rate of the reaction. Thus, the reaction might proceed through a carbocation intermediate.

To establish the synthetic utility of our method, a few reactions were envisaged (Scheme 4.13). Initially, BF_3•OEt_2/Et_3SiH mediated reaction of **3a** was performed. To our surprise, in this reaction, presumably dimethyl-2-hydroxymalonate was eliminated, and disubstituted furan **5** is formed in 85% yield. Similarly, **6** was formed from **3g** in 77% yield. Also, LiCl treatment resulted in the removal of one ester group and thus, product **7** was generated as 1:1 diastereomeric mixture in 63% combined yield. Likewise, **8** was also formed in 64% yield. It was inspected that this synthetic methodology was applicable for substrates bearing electron withdrawing and electron-donating groups.



7, Ar = Ph, 1:1 dr, 63%
8, Ar = 4-ClC_6H_4, 1:1 dr, 64%

3a, Ar = Ph
3g, Ar = 4-ClC_6H_4

5, Ar = Ph, 85%
6, Ar = 4-ClC_6H_4, 77%

Scheme 4.13. Synthetic transformations of **3a** and **3g**

In summary, we have developed a convenient synthesis of 2,5-disubstituted furan by reaction between γ-hydroxyenones and oxirane 1,1-diesters. The reaction was catalyzed by commercially available Lewis acid Sc(OTf)$_3$ and demonstrates the expedient formation of 2-arylfurans from γ-hydroxyenones. The furan products having two different substitutions at the 2- and 5-positions are important in pharmaceuticals and for natural product synthesis. Further developments of associated reactions are in progress in our laboratory.

4.6 Experimental section

General Information

For the experiments, all starting materials and reagents were purchased from standard commercial sources or were prepared in the laboratory. Reactions were carried out in oven dried glassware under an argon atmosphere with magnetic stirring. Dichloromethane was distilled over CaH_2 under argon and stored over 4Å molecular sieves. All other solvents and reagents were purified according to standard procedures. Organic solvents were dried over anhydrous Na_2SO_4 and concentrated in a rotary evaporator under reduced pressure. Reactions were monitored by TLC on silica gel GF-254 using a combination of hexane and ethyl acetate as eluents. For column chromatography silica gel (60-120 mesh size) was used.

^1H NMR spectra were recorded on a 400 MHz and 600 MHz spectrometer at 295 K in $CDCl_3$; chemical shift values (δ, ppm) and coupling constants (Hz) were reported in the standard fashion with reference to either tetramethylsilane (TMS) (δ(H) 0.00 ppm) or $CHCl_3$ (δ(H) 7.26 ppm). ^{13}C NMR spectra were recorded on a 100 MHz and 150 MHz spectrometer at 298 K in $CDCl_3$; chemical shifts (δ, ppm) were reported relative to $CHCl_3$ (δ(C) 77.23 ppm), central line of triplet. In ^{13}C NMR the nature of the carbons (C, CH, CH_2, and CH_3) were determined by recording the DEPT-135 spectra. In ^1H NMR, the following abbreviations are used throughout: s = singlet, d = doublet, t = triplet, q = quartet, qui = quintet, m = multiplet, and br s = broad singlet. IR spectra were recorded on an FT-IR Instrument at normal temperature by making KBr pellet and grinding the sample with KBr (IR Grade). High resolution mass spectra (HRMS) were recorded in Q-TOF using electron spray ionization (ESI) technique. Melting points were measured using a Mel-Tem capillary melting point apparatus.

Single crystal X-ray data were collected using Bruker SMART APEXII CCD diffractometer, which is equipped with 1.75 kW sealed-tube Mo-Kα irradiation (λ = 0.71073 Å) at 298(2) K and the structure was solved by direct methods using SHELXS-2014 (Göttingen, Germany) and refined with full-matrix least-squares on F^2 using SHELXL-2014.

A. General procedure for the synthesis of *trans*-γ-hydroxyenones 1a-1o

Trans-γ-hydroxyenones were prepared according to the reported procedure.[19]

B. General Procedure for the Synthesis of DA-oxiranes 2a-2p

All DA-oxiranes were synthesized following literature reported procedures.[16, 20]

C. General procedure for the synthesis of furan products 3a-3z''''

Under argon atmosphere, a mixture of *trans*-γ-hydroxyenones **1** (0.1 mmol), $Sc(OTf)_3$ (20 mol %) and DCM (0.25 mL) was stirred at 50 °C for 30 to 120 min. The progress of the reaction was monitored by TLC using ethyl acetate and hexane. The reaction mixture was then cooled to room temperature, and a solution of oxirane **2** (0.2 mmol) in DCM (0.25 mL) was added by a syringe. The resultant mixture was then stirred at 50 °C for the appropriate time. After completion, the reaction was allowed to cool to room temperature, and the product was purified by silica gel column chromatography using 15% ethyl acetate and hexane as an eluent to obtain the title product (**3**).

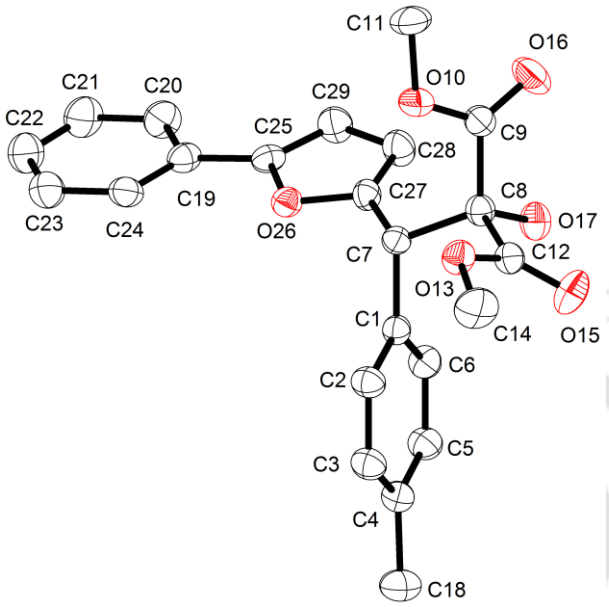
D. General procedure for the synthesis of compounds 5 and 6

To a stirred solution of **3a**/**3g** (0.1 mmol) in DCE (2 mL), triethyl silane (0.33 mmol) and $BF_3{\cdot}Et_2O$ (0.3 mmol) were added. The reaction mixture was stirred at 75 °C for 20-24 h. After that, the reaction mixture was quenched with aqueous $NaHCO_3$ and extracted with DCM. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography to obtain the desired product **6**/**7**.

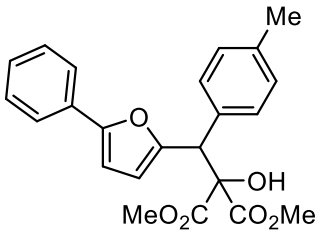
E. General procedure for the synthesis of compounds 7 and 8

To a stirred solution of **3a**/**3g** (0.1 mmol) in DMSO (0.5 mL), LiCl (3 equiv.) and 1 drop of H_2O was added to it and then the reaction mixture was placed at 110 °C for 24-30 h. Water was added, and the mixture was extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography to obtain the desired product **8**/**9**.

Crystal structure of compound 3a



ORTEP crystal structure



3a

Table 1. Crystal data and structure refinement for compound 3a

Parameters	3a
CCDC No.	1522494
Empirical formula	$C_{23}H_{22}O_6$
Formula weight	394.41
Crystal habit, colour	needle / white
Crystal size, mm^3	0.30× 0.22 × 0.18
Temperature, *T*	293(2) K
Wavelength, λ (Å)	0.71073
Crystal system	monoclinic
Space group	*'P 2₁/c'*
Unit cell dimensions	*a* = 12.2622(10) Å *b* = 16.1230(14) Å *c* = 10.5218(8) Å

	α = 90.00°, β = 97.120(8)°, γ = 90.00°
Volume, V (Å^3)	2064.2(3)
Z	4
Calculated density, Mg/m^3	1.269
Absorption coefficient, μ (mm^{-1})	0.092
F(000)	832
θ range for data collection	3.03° to 25.00°
Limiting indices	$-14 \le h \le 14$, $-17 \le k \le 19$, $-12 \le l \le 12$
Reflection collected/unique	7787/3621 [R(int) = 0.0464]
Completeness to θ	99.8 % (θ = 25.00°)
Max. and min. transmission	0.984/0.976
Refinement method	'SHELXL-97 (Sheldrick, 1997)'
Data/restraints/parameters	3621/0/274
Goodness of fit on F^2	1.056
Final R indices [$I > 2\sigma(I)$]	$R1$ = 0.0587, $wR2$ = 0.1353
R indices (all data)	$R1$ = 0.1038, $wR2$ = 0.1671
Largest diff. peak and hole	0.176 and –0.186e·Å^{-3}

4.7 References

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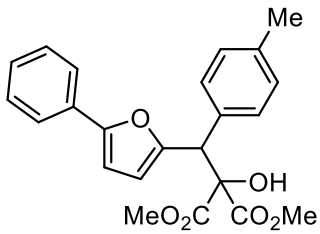
17. CCDC 1522494 contains the crystallographic data for **3a**. The data can be obtained from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif
18. For related formation of 2-alkyl/2-aryl/3-acyl furans, see: (a) Iriye, R.; Uno, T.; Ohwa, I.; Konishi, A. *Agric. Biol. Chem*. **1990**, *54*, 1841. (b) Bailey, P. S.; Waggoner, J. V.; Nowlin, G.; Rushton, G. L. *J. Am. Chem. Soc*. **1954**, *76*, 2249. (c) Sammond, D. M.; Sammakia, T. *Tetrahedron Lett*. **1996**, *37*, 6065. (d) Greatrex, B.W.; Kimber, M. C.; Taylor, D. K.; Fallon, G.; Tiekink, E. R. T. *J. Org. Chem*. **2002**, *67*, 5307. (e) Boto, A.; Hernández, D.; Hernández, R. *Org. Lett*. **2007**, *9*, 1721.
19. (a) Sada, M.; Ueno, S.; Asano, K.; Nomura, K.; Matsubara, S. *Synlett* **2009**, 724. (b) Silva, F. P. L.; Cirqueira, M. L.; Martins, F. T.; Vasconcellos, M. L. A. A. *J. Mol. Struct*. **2013**, *1052*, 189. (c) Mondal, K.; Mondal, B.; Pan, S. C. *J. Org. Chem*. **2016**, *81*, 4835.
20. Yadav, V. K.; Kapoor, K. K. *Tetrahedron Lett*. **1994**, *35*, 9481.

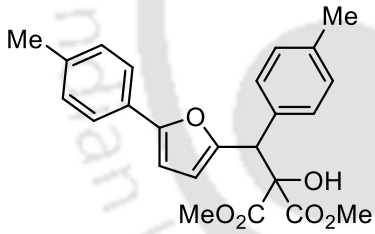
4.8 Characterization Data of Products

Dimethyl 2-hydroxy-2-((5-phenylfuran-2-yl) (p-tolyl)methyl)malonate (3a)



This compound was prepared according to the general procedure C. Reaction was completed after 60 min. Analytical TLC on silica gel using 18% ethyl acetate/hexane. White solid (27 mg, yield: 68%); **Mp:** 148-149 ^{o}C; **^{1}H NMR (400 MHz, CDCl$_3$):** δ 7.57 (d, *J* = 7.4 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.34 (t, *J* = 7.7 Hz, 2H), 7.21 (t, *J* = 7.4 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 2H), 6.53 (d, *J* = 3.3 Hz, 1H), 6.25 (d, *J* = 3.3 Hz, 1H), 5.18 (s, 1H), 4.06 (s, 1H), 3.86 (s, 3H), 3.66 (s, 3H), 2.32 (s, 3H); **^{13}C NMR (100 MHz, CDCl$_3$):** δ 170.2, 169.5, 153.1, 152.8, 137.7, 133.0, 131.0, 130.0, 129.2, 128.8, 127.3, 123.8, 110.9, 106.0, 82.1, 54.1, 53.8, 50.0, 21.4; **FT-IR (thin film):** 3484, 2953, 1754, 1734, 1513, 1435, 1247, 1218, 1182, 1141, 1022, 936, 769, 724, 687 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{23}H_{26}NO_6$ $[M+NH_4]^+$ 412.1755; found: 412.1755.

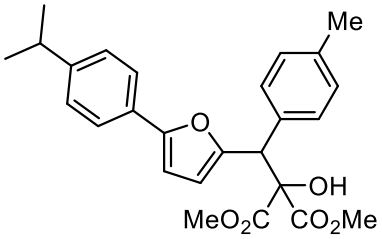
Dimethyl 2-hydroxy-2-(p-tolyl(5-p-tolylfuran-2-yl)methyl)malonate (3b)



This compound was prepared according to the general procedure C. Reaction was completed after 75 min. Analytical TLC on silica gel using 18% ethyl acetate/hexane. White solid (21 mg, yield: 51%); **Mp:** 137-138 ^{o}C; **^{1}H NMR (600 MHz, CDCl$_3$):** δ 7.46 (d, *J* = 8.1 Hz, 2H), 7.39 (d, *J* = 8.1 Hz, 2H), 7.15 (d, *J* = 8.0 Hz, 2H), 7.11 (d, *J* = 7.9 Hz, 2H), 6.46 (d, *J* = 3.3 Hz, 1H), 6.23 (d, *J* = 3.3 Hz, 1H), 5.17 (s, 1H), 4.03 (s, 1H), 3.85 (s, 3H), 3.66 (s, 3H), 2.34 (s, 3H), 2.32 (s, 3H); **^{13}C NMR (150 MHz, CDCl$_3$):** δ 170.3, 169.5, 153.4, 152.4, 137.6, 137.1, 133.18, 130.0, 129.5, 129.2, 128.4, 123.8, 110.8, 105.3, 82.2, 54.1, 53.7, 50.1, 21.4, 21.3; **FT-IR (thin film):** 3505, 2961, 1750, 1435, 1288, 1231, 1190, 1137, 936, 793, 683 cm^{-1}; **HRMS (+ESI):** Calcd for $[M+NH_4]^+$ $C_{24}H_{28}NO_6$ 426.1911; found: 426.1914.

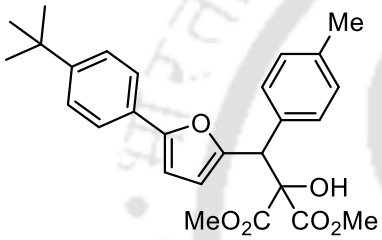
Dimethyl 2-hydroxy-2-((5-(4-isopropylphenyl) furan-2-yl)(p-tolyl)methyl)malonate (3c)

This compound was prepared according to the general procedure C. Reaction was completed after 60 min. Analytical TLC on silica gel using 15% ethyl acetate/hexane.



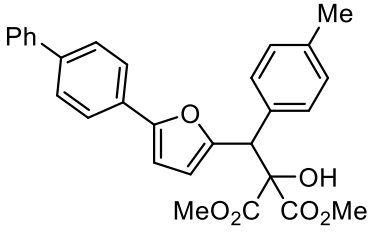
White solid (28 mg, yield: 64%); **Mp:** 171-172 °C; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.49 (d, *J* = 8.2 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.20 (d, *J* = 8.2 Hz, 2H), 7.11 (d, *J* = 7.9 Hz, 2H), 6.46 (d, *J* = 3.3 Hz, 1H), 6.22 (d, *J* = 3.2 Hz, 1H), 5.17 (s, 1H), 4.03 (s, 1H), 3.85 (s, 3H), 3.65 (s, 3H), 2.89 (dt, *J* = 13.8, 6.9 Hz, 1H), 2.31 (s, 3H), 1.25 (d, *J* = 6.9 Hz, 6H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 170.3, 169.5, 153.5, 152.5, 148.2, 137.6, 133.3, 130.0, 129.2, 128.8, 126.9, 123.9, 110.8, 105.3, 82.2, 54.0, 53.7, 50.1, 34.1, 24.1, 21.3; **FT-IR (thin film):** 3488, 2957, 1754, 1435, 1284, 1243, 1223, 1178, 1141, 1018, 936, 781 cm^{-1}; **HRMS (+ESI):** Calcd for $[M+NH_4]^+$ $C_{26}H_{32}NO_6$ 454.2224; found: 454.2224.

Dimethyl 2-((5-(4-tert-butylphenyl)furan-2-yl)(p-tolyl)methyl)-2-hydroxymalonate (3d)



This compound was prepared according to the general procedure C. Reaction was completed after 75 min. Analytical TLC on silica gel using 18% ethyl acetate/hexane. White amorphous (23 mg, yield: 51%); **Mp:** 180-181 °C; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.50 (d, *J* = 8.1 Hz, 2H), 7.38 (t, *J* = 7.6 Hz, 4H), 7.11 (d, *J* = 7.7 Hz, 2H), 6.47 (d, *J* = 2.9 Hz, 1H), 6.22 (d, *J* = 2.6 Hz, 1H), 5.17 (s, 1H), 4.03 (s, 1H), 3.86 (s, 3H), 3.66 (s, 3H), 2.32 (s, 3H), 1.32 (s, 9H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 170.3, 169.5, 153.3, 152.4, 150.4, 137.6, 133.2, 130.0, 129.2, 128.3, 125.7, 123.6, 110.8, 105.4, 82.2, 54.1, 53.7, 50.1, 34.8, 31.4, 21.3; **FT-IR (thin film):** 3488, 2953, 1754, 1435, 1284, 1247, 1223, 1178, 1141, 1022, 936, 781, 732 cm^{-1}; **HRMS (+ESI):** Calcd for $[M+NH_4]^+$ $C_{27}H_{34}NO_6$ 468.2381; found: 468.2380.

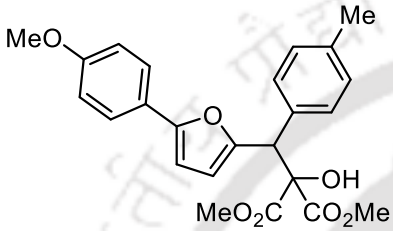
Dimethyl 2-((5-(4-biphenyl) furan-2-yl)(p-tolyl)methyl)-2-hydroxymalonate (3e)



This compound was prepared according to the general procedure C. Reaction was completed after 105 min. Analytical TLC on silica gel using 15% ethyl acetate/hexane. White solid (28 mg, yield: 59%); **Mp:** 169-170 °C; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.65 (d, *J* = 8.2 Hz, 2H), 7.60 (t, *J* = 8.5 Hz, 4H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.35 (t, *J* = 7.4 Hz, 1H), 7.13 (d, *J* = 7.8 Hz, 2H), 6.57 (d, *J* = 3.3 Hz, 1H), 6.29 (d, *J* =

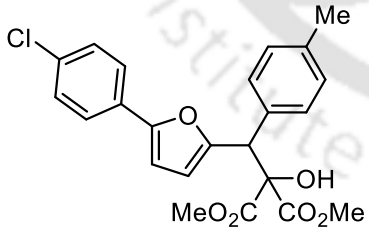
2.7 Hz, 1H), 5.21 (s, 1H), 4.06 (s, 1H), 3.87 (s, 3H), 3.67 (s, 3H), 2.33 (s, 3H); **^{13}C NMR (150 MHz, CDCl$_3$):** δ 170.3, 169.5, 153.1, 153.0, 140.9, 140.0, 137.7, 133.2, 130.1, 130.0, 129.2, 129.0, 127.5, 127.4, 127.1, 124.2, 111.0, 106.2, 82.2, 54.0, 53.7, 50.1, 21.3; **FT-IR (thin film):** 3480, 2953, 1750, 1484, 1431, 1284, 1227, 1141, 1022, 932, 781, 764, 728, 691 cm^{-1}; **HRMS (+ESI):** Calcd for [M+NH4]$^+$ $C_{29}H_{30}NO_6$ 488.2068; found: 488.2064.

Dimethyl 2-hydroxy-2-((5-(4-methoxyphenyl) furan-2-yl)(p-tolyl)methyl)malonate (3f)



This compound was prepared according to the general procedure C. Reaction was completed after 60 min. Analytical TLC on silica gel using 20% ethyl acetate/hexane. White solid (28 mg, yield: 66%); **Mp:** 144-145 ^{o}C; **^{1}H NMR (600 MHz, CDCl$_3$):** δ 7.49 (d, *J* = 8.8 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.11 (d, *J* = 7.9 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 6.38 (d, *J* = 3.3 Hz, 1H), 6.21 (d, *J* = 3.2 Hz, 1H), 5.16 (s, 1H), 4.03 (s, 1H), 3.85 (s, 3H), 3.81 (s, 3H), 3.65 (s, 3H), 2.31 (s, 3H); **^{13}C NMR (150 MHz, CDCl$_3$):** δ 170.3, 169.6, 159.1, 153.3, 152.1, 137.6, 133.3, 130.0, 129.2, 125.3, 124.3, 114.3, 110.8, 104.4, 82.2, 55.5, 54.0, 53.7, 50.1, 21.3; **FT-IR (thin film):** 3484, 2949, 1758, 1497, 1431, 1284, 1243, 1214, 1137, 1014, 936, 846, 781, 728, 679 cm^{-1}; **HRMS (+ESI):** Calcd for [M+NH$_4$]$^+$ $C_{24}H_{28}NO_7$ 442.1860; found: 442.1864.

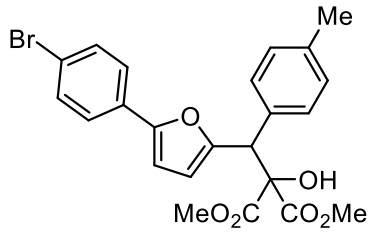
Dimethyl 2-((5-(4-chlorophenyl) furan-2-yl)(p-tolyl)methyl)-2-hydroxymalonate (3g)



This compound was prepared according to the general procedure C. Reaction was completed after 75 min. Analytical TLC on silica gel using 18% ethyl acetate/hexane. White solid (22 mg, yield: 56%); **Mp:** 136-137 ^{o}C; **^{1}H NMR (600 MHz, CDCl$_3$):** δ 7.48 (d, *J* = 8.5 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.5 Hz, 2H), 7.11 (d, *J* = 7.8 Hz, 2H), 6.51 (d, *J* = 3.3 Hz, 1H), 6.28 (d, *J* = 3.2 Hz, 1H), 5.17 (s, 1H), 4.04 (s, 1H), 3.84 (s, 3H), 3.66 (s, 3H), 2.32 (s, 3H); **^{13}C NMR (150 MHz, CDCl$_3$):** δ 170.2, 169.5, 153.2, 152.1, 137.8, 132.9, 132.9, 129.9, 129.5, 129.3, 129.0, 125.0, 110.9, 106.5, 82.1, 54.1, 53.8, 49.9, 21.3; **FT-IR (thin film):** 3476, 2949, 1754, 1480, 1431, 1280, 1247, 1218, 1178,

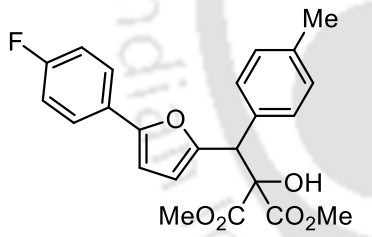
1141, 1096, 1018, 932, 838, 785, 728 cm^{-1}; **HRMS (+ESI):** Calcd for $[M+NH_4]^+$ $C_{23}H_{25}ClNO_6$ 446.1365; found: 446.1365.

Dimethyl 2-((5-(4-bromophenyl) furan-2-yl)(p-tolyl)methyl)-2-hydroxymalonate (3h)



This compound was prepared according to the general procedure C. Reaction was completed after 70 min. Analytical TLC on silica gel using 18% ethyl acetate/hexane. White solid (29 mg, yield: 61%); **Mp:** 135-136 °C; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.46 (d, *J* = 8.6 Hz, 2H), 7.42 (d, *J* = 8.6 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.11 (d, *J* = 7.9 Hz, 2H), 6.53 (d, *J* = 3.3 Hz, 1H), 6.28 (d, *J* = 3.3 Hz, 1H), 5.16 (s, 1H), 4.04 (s, 1H), 3.84 (s, 3H), 3.66 (s, 3H), 2.32 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 170.2, 169.5, 153.4, 152.1, 137.8, 133.0, 131.9, 130.0, 129.3, 125.3, 121.0, 111.0, 106.6, 82.1, 54.0, 53.8, 50.0, 21.3; **FT-IR (thin film):** 3476, 2953, 1750, 1480, 1431, 1280, 1243, 1218, 1178, 1137, 1075, 1018, 932, 781, 728, 679 cm^{-1}; **HRMS (+ESI):** Calcd for $[M+NH_4]^+$ $C_{23}H_{25}BrNO_6$ 490.0860; found: 490.0858.

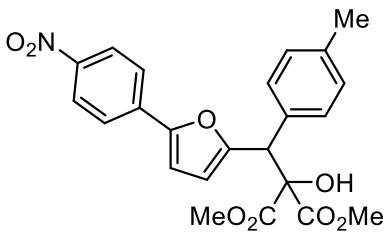
Dimethyl 2-((5-(4-fluorophenyl) furan-2-yl)(p-tolyl)methyl)-2-hydroxymalonate (3i)



This compound was prepared according to the general procedure C. Reaction was completed after 75 min. Analytical TLC on silica gel using 18% ethyl acetate/hexane. White solid (24 mg, yield: 58%); **Mp:** 147-148 °C; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.53 (dd, *J* = 8.7, 5.4 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.11 (d, *J* = 7.9 Hz, 2H), 7.03 (t, *J* = 8.7 Hz, 2H), 6.45 (d, *J* = 3.3 Hz, 1H), 6.26 (d, *J* = 3.2 Hz, 1H), 5.16 (s, 1H), 4.03 (s, 1H), 3.84 (s, 3H), 3.66 (s, 3H), 2.32 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 170.2, 169.5, 163.0, 161.4, 152.9, 152.4, 137.7, 133.1, 130.0, 129.2, 127.5, 125.6, 125.5, 115.9, 115.7, 110.8, 105.7, 82.2, 54.0, 53.7, 50.0, 21.3; **FT-IR (thin film):** 3480, 2953, 1754, 1546, 1497, 1431, 1284, 1223, 1178, 1141, 1018, 940, 842, 785, 728 cm^{-1}; **HRMS (+ESI):** Calcd for $[M+NH_4]^+$ $C_{23}H_{25}FNO_6$ 430.1660; found: 430.1663.

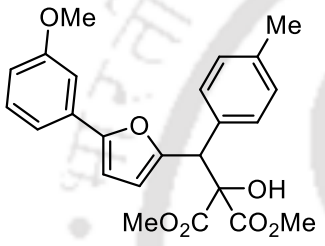
Dimethyl 2-hydroxy-2-((5-(4-nitrophenyl) furan-2-yl)(p-tolyl)methyl)malonate (3j)

This compound was prepared according to the general procedure C. Reaction was completed after 150 min. Analytical TLC on silica gel using 18% ethyl acetate/hexane.



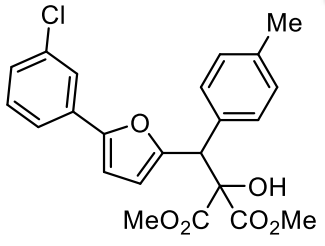
Yellow solid (11 mg, yield: 25%); **Mp:** 141-142 °C; **^{1}H NMR (600 MHz, CDCl$_3$):** δ 8.20 (d, *J* = 8.9 Hz, 2H), 7.67 (d, *J* = 8.9 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 7.12 (d, *J* = 7.9 Hz, 2H), 6.76 (d, *J* = 3.4 Hz, 1H), 6.40 (d, *J* = 3.4 Hz, 1H), 5.19 (s, 1H), 4.07 (s, 1H), 3.84 (s, 3H), 3.68 (s, 3H), 2.32 (s, 3H); **^{13}C NMR (100 MHz, CDCl$_3$):** δ 169.9, 169.4, 155.5, 150.9, 146.3, 138.1, 136.6, 132.5, 129.9, 129.4, 124.5, 123.9, 111.5, 110.2, 82.0, 54.1, 53.9, 49.8, 21.4; **FT-IR (thin film):** 3521, 2924, 1744, 1603, 1524, 1335, 1220, 1131, 853, 785, 754 cm^{-1}; **HRMS (+ESI):** Calcd for $[M+NH_4]^+$ $C_{23}H_{25}N_2O_8$ 457.1605; found: 457.1607.

Dimethyl 2-hydroxy-2-((5-(3-methoxyphenyl) furan-2-yl)(p-tolyl)methyl)malonate (3k)



This compound was prepared according to the general procedure C. Reaction was completed after 75 min. Analytical TLC on silica gel using 20% ethyl acetate/hexane. White solid (21 mg, yield: 49%); **Mp:** 148-149 °C; **^{1}H NMR (600 MHz, CDCl$_3$):** δ 7.38 (d, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.16 (d, *J* = 7.7 Hz, 1H), 7.11 (d, *J* = 7.6 Hz, 3H), 6.77 (dd, *J* = 8.1, 2.1 Hz, 1H), 6.52 (d, *J* = 3.3 Hz, 1H), 6.24 (d, *J* = 3.2 Hz, 1H), 5.18 (s, 1H), 4.04 (s, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.66 (s, 3H), 2.32 (s, 3H); **^{13}C NMR (150 MHz, CDCl$_3$):** δ 170.3, 169.5, 160.1, 153.0, 137.7, 133.1, 132.4, 130.0, 129.9, 129.2, 116.5, 113.1, 110.9, 109.3, 106.4, 82.2, 55.5, 54.0, 53.7, 50.1, 21.3; **FT-IR (thin film):** 3497, 2961, 1746, 1726, 1582, 1488, 1431, 1288, 1214, 1137, 1043, 936, 979, 724 cm^{-1}; **HRMS (+ESI):** Calcd for $[M+H]^+$ $C_{24}H_{25}O_7$ 425.1595; found: 425.1592.

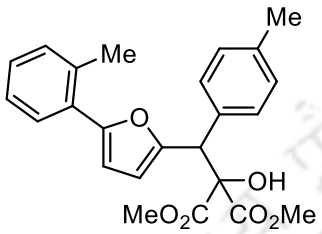
Dimethyl 2-((5-(3-chlorophenyl) furan-2-yl)(p-tolyl)methyl)-2-hydroxymalonate (3l)



This compound was prepared according to the general procedure C. Reaction was completed after 45 min. Analytical TLC on silica gel using 15% ethyl acetate/hexane. White solid (13 mg, yield: 30%); **Mp:** 166-167 °C; **^{1}H NMR (600 MHz, CDCl$_3$):** δ 7.54 (s, 1H), 7.43 (d, *J* = 7.8 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.26 (t, *J* = 7.9 Hz, 2H), 7.17 (d, *J* = 7.9 Hz, 1H), 7.12 (d, *J* = 7.9 Hz, 2H), 6.55 (d, *J* = 3.3 Hz, 1H), 6.28 (d, *J* = 3.3 Hz, 1H), 5.17 (s, 1H), 4.04 (s, 1H),

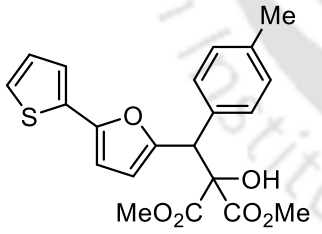
3.86 (s, 3H), 3.66 (s, 3H), 2.32 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 170.2, 169.5, 153.6, 151.7, 137.8, 134.9, 133.0, 132.7, 130.1, 130.0, 129.3, 127.2, 123.8, 121.8, 111.0, 107.1, 82.2, 54.1, 53.8, 50.0, 21.3; **FT-IR (thin film):** 3497, 2953, 1754, 1480, 1435, 1280, 1178, 1137, 1026, 932, 781 cm^{-1}; **HRMS (+ESI):** Calcd for $[M+NH_4]^+$ $C_{23}H_{25}ClNO_6$ 446.1365; found: 446.1363.

Dimethyl 2-hydroxy-2-(p-tolyl(5-o-tolylfuran-2-yl)methyl)malonate (3m)



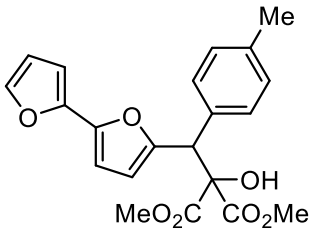
This compound was prepared according to the general procedure C. Reaction was completed after 120 min. Analytical TLC on silica gel using 15% ethyl acetate/hexane. White solid (14 mg, yield: 34%); **Mp:** 151-152 °C; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.60 (d, *J* = 7.3 Hz, 1H), 7.39 (d, *J* = 7.9 Hz, 2H), 7.24 – 7.15 (m, 3H), 7.11 (d, *J* = 7.9 Hz, 2H), 6.41 (d, *J* = 3.2 Hz, 1H), 6.27 (d, *J* = 3.2 Hz, 1H), 5.18 (s, 1H), 4.05 (s, 1H), 3.83 (s, 3H), 3.66 (s, 3H), 2.43 (s, 3H), 2.31 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 170.2, 169.6, 152.8, 152.3, 137.7, 134.5, 133.2, 131.3, 130.3, 130.0, 129.2, 127.4, 127.0, 126.1, 110.6, 109.6, 82.2, 54.1, 53.8, 50.0, 22.1, 21.3; **FT-IR (thin film):** 3509, 2965, 1746, 1722, 1439, 1288, 1231, 1190, 1137, 1026, 936, 801, 760, 724 cm^{-1}; **HRMS (+ESI):** Calcd for $[M+H]^+$ $C_{24}H_{25}O_6$ 409.1646; found: 409.1647.

Dimethyl 2-hydroxy-2-((5-(thiophen-2-yl)furan-2-yl)(p-tolyl)methyl)malonate (3n)



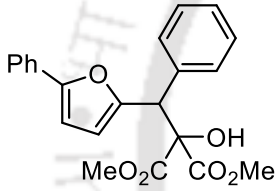
This compound was prepared according to the general procedure C. Reaction was completed after 90 min. Analytical TLC on silica gel using 15% ethyl acetate/hexane. Yellow solid (12 mg, yield: 30%); **Mp:** 141-142 °C; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.38 (d, *J* = 8.0 Hz, 2H), 7.16 (dd, *J* = 13.0, 3.9 Hz, 2H), 7.11 (d, *J* = 7.9 Hz, 2H), 7.00 – 6.98 (m, 1H), 6.37 (d, *J* = 3.3 Hz, 1H), 6.20 (d, *J* = 3.2 Hz, 1H), 5.14 (s, 1H), 4.04 (s, 1H), 3.89 (s, 3H), 3.65 (s, 3H), 2.32 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 170.2, 169.5, 152.5, 148.7, 137.7, 134.0, 133.0, 130.0, 129.2, 127.8, 124.0, 122.5, 111.0, 106.0, 82.1, 54.2, 53.7, 49.9, 21.3; **FT-IR (thin film):** 3492, 2953, 1754, 1435, 1280, 1218, 1178, 1141, 1014, 777, 703 cm^{-1}; **HRMS (+ESI):** Calcd for $[M+NH_4]^+$ $C_{21}H_{24}NSO_6$ 418.1319; found: 418.1319.

Dimethyl 2-((5-(furan-2-yl)furan-2-yl)(p-tolyl)methyl)-2-hydroxymalonate (3o)



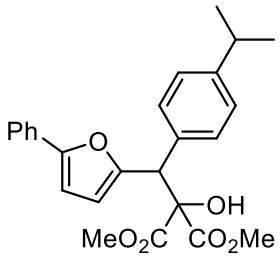
This compound was prepared according to the general procedure C. Reaction was completed after 70 min. Analytical TLC on silica gel using 15% ethyl acetate/hexane. Yellow sticky solid (8 mg, yield: 20%); **^{1}H NMR (600 MHz, CDCl$_3$):** δ 7.35 (d, *J* = 8.2 Hz, 3H), 7.10 (d, *J* = 7.8 Hz, 2H), 6.45 – 6.39 (m, 3H), 6.27 (d, *J* = 3.2 Hz, 1H), 5.15 (s, 1H), 4.03 (s, 1H), 3.85 (s, 3H), 3.66 (s, 3H), 2.31 (s, 3H); **^{13}C NMR (75 MHz, CDCl$_3$):** δ 170.1, 169.5, 152.6, 146.7, 145.8, 141.8, 137.7, 132.9, 129.9, 129.2, 111.5, 110.5, 106.1, 105.0, 82.1, 54.1, 53.8, 49.9, 21.3; **FT-IR (thin film):** 3495, 2955, 1750, 1435, 1246, 1142, 1016, 780, 748 cm^{-1}; **HRMS (+ESI):** Calcd for $[M+NH_4]^+$ $C_{21}H_{24}NO_7$ 402.1547; found: 402.1545.

Dimethyl 2-hydroxy-2-(phenyl(5-phenylfuran-2-yl)methyl)malonate (3p)



This compound was prepared according to the general procedure C. Reaction was completed after 85 min. Analytical TLC on silica gel using 15% ethyl acetate/hexane. White solid (15 mg, yield: 37%); Mp: 152-153 ^{o}C; **^{1}H NMR (600 MHz, CDCl$_3$):** δ 7.57 (d, *J* = 7.7 Hz, 2H), 7.51 (d, *J* = 7.3 Hz, 2H), 7.34 (t, *J* = 7.8 Hz, 2H), 7.31 (d, *J* = 7.5 Hz, 2H), 7.28 (d, *J* = 7.0 Hz, 1H), 7.22 (t, *J* = 7.3 Hz, 1H), 6.53 (d, *J* = 3.1 Hz, 1H), 6.26 (d, *J* = 3.0 Hz, 1H), 5.21 (s, 1H), 4.07 (s, 1H), 3.86 (s, 3H), 3.65 (s, 3H); **^{13}C NMR (150 MHz, CDCl$_3$):** δ 170.2, 169.5, 153.3, 152.6, 136.2, 131.0, 130.2, 128.8, 128.5, 128.1, 127.4, 123.8, 111.0, 106.0, 82.1, 54.1, 53.8, 50.4; **FT-IR (thin film):** 3537, 2953, 1750, 1484, 1452, 1431, 1227, 1178, 1133, 1026, 932, 793, 760, 703 cm^{-1}; **HRMS (+ESI):** Calcd for $[M+NH_4]^+$ $C_{22}H_{24}NO_6$ 398.1598; found: 398.1601.

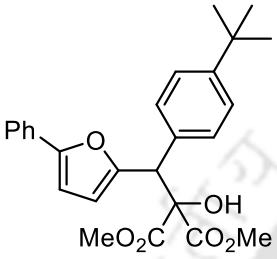
Dimethyl 2-hydroxy-2-((4-isopropylphenyl)(5-phenylfuran-2-yl)methyl)malonate (3q)



This compound was prepared according to the general procedure C. Reaction was completed after 60 min. Analytical TLC on silica gel using 15% ethyl acetate/hexane. White solid (26 mg, yield: 62%); **Mp:** 131-132 ^{o}C; **^{1}H NMR (600 MHz, CDCl$_3$):** δ 7.57 (d, *J* = 7.6 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.34 (t, *J* = 7.7 Hz, 2H), 7.21 (t, *J* = 7.4 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 2H), 6.53 (d, *J* = 3.3 Hz, 1H), 6.29

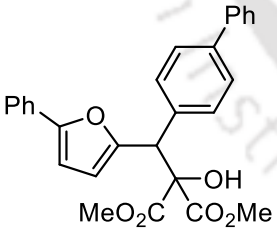
(d, *J* = 3.2 Hz, 1H), 5.19 (s, 1H), 4.05 (s, 1H), 3.85 (s, 3H), 3.66 (s, 3H), 2.87 (dt, *J* = 13.8, 6.9 Hz, 1H), 1.22 (d, *J* = 6.8 Hz, 6H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 170.3, 169.5, 153.1, 152.9, 148.5, 133.3, 131.0, 130.0, 128.8, 127.3, 126.5, 123.8, 110.9, 106.0, 82.2, 54.1, 53.7, 50.0, 33.9, 24.1, 24.1; **FT-IR (thin film):** 3497, 2961, 1754, 1717, 1431, 1284, 1231, 1169, 1137, 1026, 793, 760, 691 cm^{-1}; **HRMS (+ESI):** Calcd for $[M+NH_4]^+$ $C_{25}H_{30}NO_6$ 440.2068; found: 440.2066.

Dimethyl 2-((4-tert-butylphenyl)(5-phenylfuran-2-yl)methyl)-2-hydroxymalonate (3r)



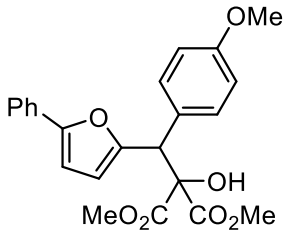
This compound was prepared according to the general procedure C. Reaction was completed after 60 min. Analytical TLC on silica gel using 15% ethyl acetate/hexane. White solid (22 mg, yield: 50%); **Mp:** 166-167 ºC; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.58 (d, *J* = 7.3 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.34 (t, *J* = 7.8 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.22 (t, *J* = 7.4 Hz, 1H), 6.53 (d, *J* = 3.3 Hz, 1H), 6.30 (d, *J* = 3.2 Hz, 1H), 5.20 (s, 1H), 4.06 (s, 1H), 3.84 (s, 3H), 3.66 (s, 3H), 1.29 (s, 9H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 170.3, 169.5, 153.1, 152.8, 150.8, 132.9, 131.0, 129.8, 128.8, 127.3, 125.4, 123.8, 110.9, 106.0, 82.2, 54.1, 53.7, 49.9, 34.7, 31.5; **FT-IR (thin film):** 3488, 2961, 1754, 1431, 1223, 1137, 1026, 793, 760, 691 cm^{-1}; **HRMS (+ESI):** Calcd for $[M+NH_4]^+$ $C_{26}H_{32}NO_6$ 454.2224; found: 454.2221.

Dimethyl 2-((4-biphenyl)(5-phenylfuran-2-yl)methyl)-2-hydroxymalonate (3s)



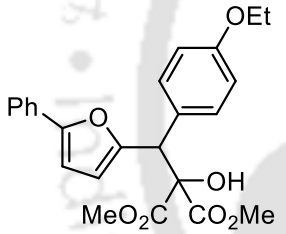
This compound was prepared according to the general procedure C. Reaction was completed after 60 min. Analytical TLC on silica gel using 15% ethyl acetate/hexane. Yellow sticky solid (33.5 mg, yield: 73%); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.62 – 7.58 (m, 6H), 7.56 (d, *J* = 8.3 Hz, 2H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.36 (t, *J* = 7.8 Hz, 3H), 7.24 (t, *J* = 7.4 Hz, 1H), 6.57 (d, *J* = 3.3 Hz, 1H), 6.33 (d, *J* = 2.6 Hz, 1H), 5.29 (s, 1H), 4.16 (s, 1H), 3.88 (s, 3H), 3.69 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 170.2, 169.4, 153.3, 152.5, 140.8, 140.7, 135.2, 131.0, 130.6, 128.9, 128.8, 127.5, 127.4, 127.2, 127.1, 123.8, 111.0, 106.0, 82.1, 54.2, 53.8, 50.0; **FT-IR (thin film):** 3517, 2920, 1738, 1484, 1431, 1235, 1129, 760, 736, 691 cm^{-1}; **HRMS (+ESI):** Calcd for $[M+NH_4]^+$ $C_{28}H_{28}NO_6$ 474.1911; found: 474.1908.

Dimethyl 2-hydroxy-2-((4-methoxyphenyl)(5-phenylfuran-2-yl)methyl)malonate (3t)



This compound was prepared according to the general procedure C. Reaction was completed after 60 min. Analytical TLC on silica gel using 20% ethyl acetate/hexane. White solid (32 mg, yield: 78%); **Mp:** 131-132 °C; **^{1}H NMR (600 MHz, CDCl$_3$):** δ 7.57 (d, *J* = 7.4 Hz, 2H), 7.43 (d, *J* = 8.7 Hz, 2H), 7.34 (t, *J* = 7.7 Hz, 2H), 7.22 (t, *J* = 7.4 Hz, 1H), 6.84 (d, *J* = 8.7 Hz, 2H), 6.52 (d, *J* = 3.3 Hz, 1H), 6.23 (d, *J* = 3.2 Hz, 1H), 5.17 (s, 1H), 4.04 (s, 1H), 3.86 (s, 3H), 3.79 (s, 3H), 3.66 (s, 3H); **^{13}C NMR (150 MHz, CDCl$_3$):** δ 170.3, 169.5, 159.4, 153.2, 153.0, 131.3, 131.0, 128.8, 128.2, 127.3, 123.8, 113.8, 110.8, 106.0, 82.2, 55.4, 54.1, 53.7, 49.6; **FT-IR (thin film):** 3492, 2953, 1754, 1730, 1611, 1509, 1435, 1243, 1178, 1141, 1.26, 936, 793, 769, 695, 687 cm^{-1}; **HRMS (+ESI):** Calcd for $[M+NH_4]^+$ $C_{23}H_{26}NO_7$ 428.1704; found: 428.1702.

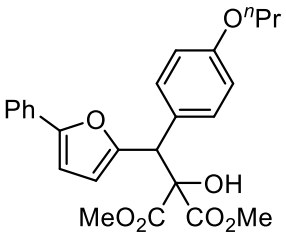
Dimethyl 2-((4-ethoxyphenyl)(5-phenylfuran-2-yl)methyl)-2-hydroxymalonate (3u)



This compound was prepared according to the general procedure C. Reaction was completed after 60 min. Analytical TLC on silica gel using 20% ethyl acetate/hexane. White solid (33 mg, yield: 77%); **Mp:** 91-92 °C; **^{1}H NMR (600 MHz, CDCl$_3$):** δ 7.56 (d, *J* = 7.3 Hz, 2H), 7.41 (d, *J* = 8.7 Hz, 2H), 7.34 (t, *J* = 7.8 Hz, 2H), 7.21 (t, *J* = 7.4 Hz, 1H), 6.83 (d, *J* = 8.7 Hz, 2H), 6.52 (d, *J* = 3.3 Hz, 1H), 6.22 (d, *J* = 2.9 Hz, 1H), 5.16 (s, 1H), 4.05 (s, 1H), 4.00 (q, *J* = 7.0 Hz, 2H), 3.86 (s, 3H), 3.66 (s, 3H), 1.40 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (150 MHz, CDCl$_3$):** δ 170.3, 169.5, 158.7, 153.1, 153.0, 131.2, 131.0, 128.8, 128.0, 127.3, 123.8, 114.3, 110.8, 106.0, 82.2, 63.5, 54.1, 53.7, 49.7, 15.0; **FT-IR (thin film):** 3484, 2953, 1754, 1730, 1611, 1509, 1435, 1231, 1174, 1137, 1084, 1026, 936, 793, 764, 683, 654 cm^{-1}; **HRMS (+ESI):** Calcd for $[M+H]^+$ $C_{24}H_{25}O_7$ 425.1595; found: 425.1599.

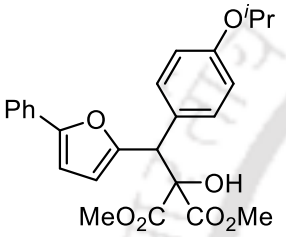
Dimethyl 2-hydroxy-2-((5-phenylfuran-2-yl)(4-propoxyphenyl)methyl)malonate (3v)

This compound was prepared according to the general procedure C. Reaction was completed after 60 min. Analytical TLC on silica gel using 20% ethyl acetate/hexane. White solid (32.5 mg, yield: 74%); **Mp:** 92-93 °C; **^{1}H NMR (600 MHz, CDCl$_3$):** δ 7.57 (d, *J* = 7.8 Hz, 2H), 7.41 (d, *J* = 8.7 Hz, 2H), 7.34 (t, *J* = 7.7 Hz, 2H), 7.21 (t, *J* = 7.4 Hz,



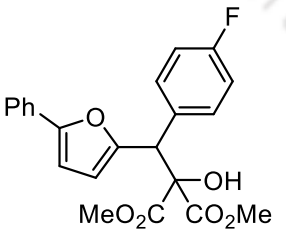
1H), 6.84 (d, *J* = 8.7 Hz, 2H), 6.53 (d, *J* = 3.3 Hz, 1H), 6.23 (d, *J* = 2.9 Hz, 1H), 5.16 (s, 1H), 4.05 (s, 1H), 3.89 (t, *J* = 6.5 Hz, 2H), 3.86 (s, 3H), 3.66 (s, 3H), 1.82 – 1.76 (m, 2H), 1.03 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR (150 MHz, CDCl$_3$):** δ 170.3, 169.5, 159.0, 153.2, 153.0, 131.2, 131.1, 128.8, 127.9, 127.3, 123.9, 114.4, 110.8, 106.0, 82.2, 69.6, 54.1, 53.7, 49.7, 22.8, 10.7; **FT-IR (thin film):** 3542, 2957, 1750, 1431, 1255, 1182, 1129, 1026, 957, 805, 789, 756, 691 cm^{-1}; **HRMS (+ESI):** Calcd for $[M+NH_4]^+$ $C_{25}H_{30}NO_7$ 456.2017; found: 456.2019.

Dimethyl 2-hydroxy-2-((4-isopropoxyphenyl)(5-phenylfuran-2-yl)methyl)malonate(3w)



This compound was prepared according to the general procedure C. Reaction was completed after 60 min. Analytical TLC on silica gel using 20% ethyl acetate/hexane. White solid (33 mg, yield: 75%); **Mp:** 115-116 ^{o}C; **^{1}H NMR (600 MHz, CDCl$_3$):** δ 7.57 (d, *J* = 7.4 Hz, 2H), 7.40 (d, *J* = 8.7 Hz, 2H), 7.34 (t, *J* = 7.8 Hz, 2H), 7.21 (t, *J* = 7.4 Hz, 1H), 6.81 (d, *J* = 8.7 Hz, 2H), 6.53 (d, *J* = 3.3 Hz, 1H), 6.24 (d, *J* = 3.2 Hz, 1H), 5.15 (s, 1H), 4.52 (dt, *J* = 12.1, 6.1 Hz, 1H), 4.05 (s, 1H), 3.85 (s, 3H), 3.66 (s, 3H), 1.32 (dd, *J* = 6.0, 2.7 Hz, 6H); **^{13}C NMR (150 MHz, CDCl$_3$):** δ 170.3, 169.5, 157.7, 153.2, 153.0, 131.3, 131.1, 128.8, 127.9, 127.3, 123.8, 115.6, 110.8, 106.0, 82.3, 69.9, 54.1, 53.7, 49.7, 22.3; **FT-IR (thin film):** 3546, 2981, 1738, 1607, 1509, 1431, 1235, 1178, 1129, 1026, 953, 793, 760, 691 cm^{-1}; **HRMS (+ESI):** Calcd for $[M+NH_4]^+$ $C_{25}H_{30}NO_7$ 456.2017; found: 456.2018.

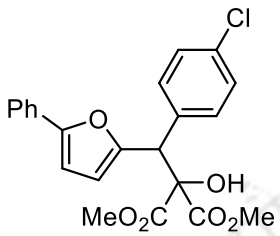
Dimethyl 2-((4-fluorophenyl)(5-phenylfuran-2-yl)methyl)-2-hydroxymalonate (3x)



This compound was prepared according to the general procedure C. Reaction was completed after 80 min. Analytical TLC on silica gel using 15% ethyl acetate/hexane. White solid (16 mg, yield: 35%); **Mp:** 120-121 ^{o}C; **^{1}H NMR (600 MHz, CDCl$_3$):** δ 7.56 (d, *J* = 7.3 Hz, 2H), 7.50 (dd, *J* = 8.7, 5.5 Hz, 2H), 7.35 (t, *J* = 7.8 Hz, 2H), 7.23 (t, *J* = 7.4 Hz, 1H), 7.00 (t, *J* = 8.7 Hz, 2H), 6.53 (d, *J* = 3.4 Hz, 1H), 6.22 (d, *J* = 3.2 Hz, 1H), 5.21 (s, 1H), 4.08 (s, 1H), 3.86 (s, 3H), 3.66 (s, 3H); **^{13}C NMR (150 MHz, CDCl$_3$):** δ 170.2, 169.3, 163.5, 161.8, 152.9 (d, *J* = 157.5 Hz), 132.0, 131.9 (d, *J* = 7.5 Hz), 130.9, 128.8, 127.5, 123.8, 115.3 (d, *J* = 22.5 Hz), 111.0, 106.0, 82.0,

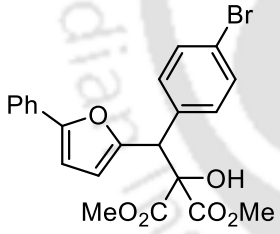
54.2, 53.8, 49.5; **FT-IR (thin film):** 3476, 2953, 1754, 1730, 1603, 1505, 1431, 1268, 1218, 1137, 1026, 850, 805, 769, 699, 560 cm^{-1}; **HRMS (+ESI):** Calcd for $[M+NH_4]^+$ $C_{22}H_{23}FNO_6$ 416.1504; found: 416.1504.

Dimethyl 2-((4-chlorophenyl)(5-phenylfuran-2-yl)methyl)-2-hydroxymalonate (3y)



This compound was prepared according to the general procedure C. Reaction was completed after 70 min. Analytical TLC on silica gel using 15% ethyl acetate/hexane. White solid (23.5 mg, yield: 36%); **Mp:** 138-139 ^oC; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.56 (d, *J* = 7.4 Hz, 2H), 7.47 (d, *J* = 8.5 Hz, 2H), 7.35 (t, *J* = 7.8 Hz, 2H), 7.29 (d, *J* = 8.5 Hz, 2H), 7.23 (t, *J* = 7.4 Hz, 1H), 6.53 (d, *J* = 3.3 Hz, 1H), 6.23 (d, *J* = 3.2 Hz, 1H), 5.19 (s, 1H), 4.09 (s, 1H), 3.86 (s, 3H), 3.67 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 170.1, 169.2, 153.8, 152.0, 134.8, 134.0, 131.6, 130.9, 128.8, 128.7, 127.5, 123.8, 111.1, 106.0, 81.9, 54.3, 53.9, 49.6; **FT-IR (thin film):** 3480, 2953, 1754, 1493, 1280, 1243, 1178, 1137, 1092, 1022936, 764, 724, 687 cm^{-1}; **HRMS (+ESI):** Calcd for $[M+NH_4]^+$ $C_{22}H_{23}ClNO_6$ 432.1208; found: 432.1209.

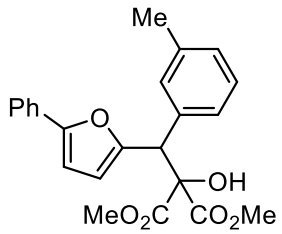
Dimethyl 2-((4-bromophenyl)(5-phenylfuran-2-yl)methyl)-2-hydroxymalonate (3z)



This compound was prepared according to the general procedure C. Reaction was completed after 75 min. Analytical TLC on silica gel using 15% ethyl acetate/hexane. Yellow solid (19 mg, yield: 36%); **Mp:** 156-157 ^oC; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.56 (d, *J* = 7.4 Hz, 2H), 7.44 (d, *J* = 8.5 Hz, 2H), 7.40 (d, *J* = 8.6 Hz, 2H), 7.35 (t, *J* = 7.8 Hz, 2H), 7.23 (t, *J* = 7.4 Hz, 1H), 6.53 (d, *J* = 3.3 Hz, 1H), 6.23 (d, *J* = 3.2 Hz, 1H), 5.18 (s, 1H), 4.09 (s, 1H), 3.86 (s, 3H), 3.67 (s, 3H), 1.58 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 170.1, 169.2, 153.5, 152.0, 135.3, 131.9, 131.7, 130.9, 128.9, 127.5, 123.8, 122.3, 111.1, 106.0, 81.9, 54.3, 53.9, 49.6; **FT-IR (thin film):** 3497, 2961, 1750, 1722, 1546, 1488, 1235, 1190, 1137, 1010, 932, 756, 687 cm^{-1}; **HRMS (+ESI):** Calcd for $[M+NH_4]^+$ $C_{22}H_{23}BrNO_6$ 476.0703; found: 476.0700.

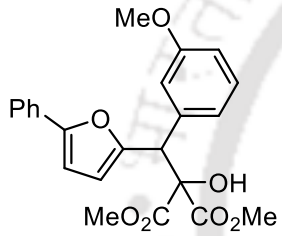
Dimethyl 2-hydroxy-2-((5-phenylfuran-2-yl)(m-tolyl)methyl)malonate (3z')

This compound was prepared according to the general procedure C. Reaction was completed after 90 min. Analytical TLC on silica gel using 15% ethyl acetate/hexane.



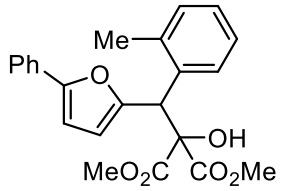
Brownish liquid (16 mg, yield: 40%); **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 7.57 (d, *J* = 7.4 Hz, 2H), 7.34 (t, *J* = 7.8 Hz, 2H), 7.30 (d, *J* = 7.0 Hz, 2H), 7.22 (d, *J* = 7.4 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 7.09 (d, *J* = 7.5 Hz, 1H), 6.53 (d, *J* = 3.3 Hz, 1H), 6.27 (d, *J* = 3.3 Hz, 1H), 5.18 (s, 1H), 4.06 (s, 1H), 3.86 (s, 3H), 3.66 (s, 3H), 2.33 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 170.2, 169.5, 153.2, 152.7, 138.0, 136.0, 131.0, 130.84, 128.8, 128.8, 128.3, 127.3, 127.1, 123.8, 110.9, 106.0, 82.1, 54.1, 53.7, 50.3, 21.7; **FT-IR (thin film):** 3484, 2924, 1742, 1607, 1784, 1431, 1231, 1133, 1022, 760, 711 cm^{-1}; **HRMS (+ESI):** Calcd for $[M+NH_4]^+$ $C_{23}H_{26}NO_6$ 412.1755; found: 412.1756.

Dimethyl 2-hydroxy-2-((3-methoxyphenyl)(5-phenylfuran-2-yl)methyl)malonate (3z'')



This compound was prepared according to the general procedure C. Reaction was completed after 70 min. Analytical TLC on silica gel using 15% ethyl acetate/hexane. Colorless sticky liquid (23 mg, yield: 56%); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.57 (d, *J* = 7.6 Hz, 2H), 7.34 (t, *J* = 7.8 Hz, 2H), 7.23 – 7.20 (m, *J* = 7.9, 4.0 Hz, 2H), 7.08 (d, *J* = 6.8 Hz, 2H), 6.84 – 6.80 (m, 1H), 6.53 (d, *J* = 3.3 Hz, 1H), 6.28 (d, *J* = 3.3 Hz, 1H), 5.19 (s, 1H), 4.07 (s, 1H), 3.85 (s, 3H), 3.78 (s, 3H), 3.67 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 170.2, 169.5, 159.6, 153.2, 152.5, 137.6, 131.0, 129.4, 128.8, 127.3, 123.8, 122.5, 115.9, 113.4, 111.0, 106.0, 82.1, 55.4, 54.1, 53.8, 50.3; **FT-IR (thin film):** 3464, 2924, 1742, 1603, 1488, 1435, 1231, 1137, 1047, 760 cm^{-1}; **HRMS (+ESI):** Calcd for $[M+NH_4]^+$ $C_{23}H_{26}NO_7$ 428.1704; found: 428.1703.

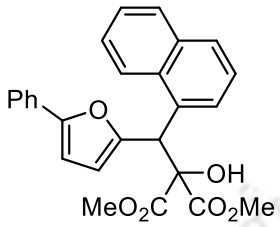
Dimethyl 2-hydroxy-2-((5-phenylfuran-2-yl)(o-tolyl)methyl)malonate (3z''')



This compound was prepared according to the general procedure C. Reaction was completed after 65 min. Analytical TLC on silica gel using 15% ethyl acetate/hexane. Colorless sticky solid (16 mg, yield: 40%); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.88 (d, *J* = 5.3 Hz, 1H), 7.55 (d, *J* = 7.6 Hz, 2H), 7.35 (t, *J* = 7.7 Hz, 2H), 7.22 (t, *J* = 7.4 Hz, 1H), 7.19 – 7.15 (m, 3H), 6.49 (d, *J* = 3.3 Hz, 1H), 5.99 (d, *J* = 3.2 Hz, 1H), 5.51 (s, 1H), 4.17 (s, 1H), 3.95 (s, 3H), 3.55 (s, 3H), 2.45 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 170.7, 169.5, 153.4, 152.6, 136.9, 135.4, 131.09, 130.5, 129.2, 128.8, 127.8, 127.4, 126.5,

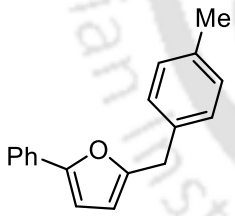
123.8, 111.5, 106.0, 82.2, 54.3, 53.5, 45.0, 20.1; **FT-IR (thin film):** 3505, 2957, 1754, 1730, 1542, 1484, 1431, 1272, 1210, 1141, 1026, 965, 764, 732 cm^{-1}; **HRMS (+ESI):** Calcd for $[M+NH_4]^+$ $C_{23}H_{26}NO_6$ 412.1755; found: 412.1757.

Dimethyl 2-hydroxy-2-((naphthalen-1-yl)(5-phenylfuran-2-yl)methyl)malonate (3z''')



This compound was prepared according to the general procedure C. Reaction was completed after 70 min. Analytical TLC on silica gel using 18% ethyl acetate/hexane. Yellow sticky solid (28 mg, yield: 65%); **^{1}H NMR (600 MHz, CDCl$_3$):** δ 8.26 (d, *J* = 8.6 Hz, 1H), 8.07 (d, *J* = 7.3 Hz, 1H), 7.86 (d, *J* = 7.9 Hz, 1H), 7.80 (d, *J* = 8.2 Hz, 1H), 7.57 – 7.53 (m, 3H), 7.47 (dd, *J* = 15.4, 7.9 Hz, 2H), 7.34 (t, *J* = 7.8 Hz, 2H), 7.22 (t, *J* = 7.5 Hz, 1H), 6.49 (d, *J* = 3.4 Hz, 1H), 6.19 (s, 1H), 6.08 (d, *J* = 3.3 Hz, 1H), 4.23 (s, 1H), 3.98 (s, 3H), 3.31 (s, 3H); **^{13}C NMR (150 MHz, CDCl$_3$):** δ 170.5, 169.5, 153.3, 152.8, 134.1, 132.7, 132.0, 131.0, 129.1, 128.8, 128.6, 127.6, 127.4, 126.4, 125.7, 125.6, 123.8, 123.4, 111.7, 106.1, 82.1, 54.3, 53.5, 44.1; **FT-IR (thin film):** 3456, 2957, 1754, 1435, 1272, 1218, 1137, 1026, 936, 793, 777, 760, 691 cm^{-1}; **HRMS (+ESI):** Calcd for $[M+NH_4]^+$ $C_{26}H_{26}NO_6$ 448.1755; found: 448.1753.

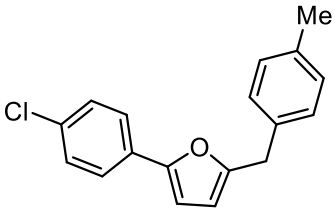
2-(4-methylbenzyl)-5-phenylfuran (5)



This compound was prepared according to the general procedure D. Reaction was completed after 24 h. Analytical TLC on silica gel using 3% ethyl acetate/hexane. Yellowish liquid (21 mg, yield: 85%); **^{1}H NMR (600 MHz, CDCl$_3$):** δ 7.63 (d, *J* = 7.7 Hz, 2H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.24 – 7.17 (m, 3H), 7.13 (d, *J* = 7.8 Hz, 2H), 6.56 (d, *J* = 3.0 Hz, 1H), 6.05 (d, *J* = 2.7 Hz, 1H), 4.00 (s, 2H), 2.34 (s, 3H); **^{13}C NMR (150 MHz, CDCl$_3$):** δ 154.9, 153.0, 136.2, 135.2, 131.3, 129.4, 128.8, 128.78, 127.1, 123.6, 108.5, 106.0, 34.5, 21.3; **FT-IR (thin film):** 2924, 1546, 1513, 1488, 1448, 1022, 789, 760, 691 cm^{-1}; **HRMS (+ESI):** Calcd for $[M+H]^+$ $C_{18}H_{17}O$ 249.1274; found: 249.1277.

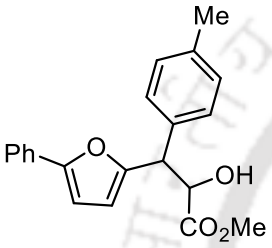
2-(4-methylbenzyl)-5-(4-chlorophenyl)furan (6)

This compound was prepared according to the general procedure D. Reaction was completed after 20 h. Analytical TLC on silica gel using 3% ethyl acetate/hexane.



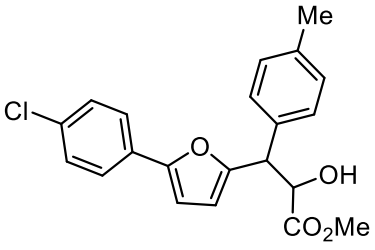
Yellow semi solid (22 mg, yield: 77%); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.53 (d, *J* = 8.6 Hz, 2H), 7.30 (d, *J* = 8.5 Hz, 2H), 7.17 (d, *J* = 7.9 Hz, 2H), 7.13 (d, *J* = 7.9 Hz, 2H), 6.53 (d, *J* = 3.2 Hz, 1H), 6.05 (d, *J* = 3.2 Hz, 1H), 3.98 (s, 2H), 2.33 (s, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 155.3, 151.9, 136.3, 134.9, 132.6, 129.8, 129.5, 128.9, 128.8, 124.9, 108.6, 106.5, 34.4, 21.3; **FT-IR (thin film):** 2924, 1514, 1482, 1461, 1094, 1016, 827 cm^{-1}; **HRMS (+ESI):** Calcd for $[M+H]^+$ $C_{18}H_{16}NClO$ 283.0884; found: 283.0083.

Methyl 2-hydroxy-3-(5-phenylfuran-2-yl)-3-p-tolylpropanoate (7)



This compound was prepared according to the general procedure E. Reaction was completed after 30 h. Analytical TLC on silica gel using 12% ethyl acetate/hexane. Yellowish liquid (21 mg, yield: 63%); **Diastereomeric ratio:** 1:1; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.61 (dd, *J* = 13.3, 7.8 Hz, 4H), 7.36 (dd, *J* = 14.4, 7.1 Hz, 7H), 7.23 (d, *J* = 7.3 Hz, 4H), 7.17 (d, *J* = 7.4 Hz, 2H), 7.14 (d, *J* = 7.3 Hz, 2H), 6.59 (d, *J* = 2.9 Hz, 1H), 6.56 (d, *J* = 2.9 Hz, 1H), 6.34 (d, *J* = 2.2 Hz, 1H), 6.19 (d, *J* = 2.3 Hz, 1H), 4.96 (d, *J* = 4.9 Hz, 1H), 4.67 (d, *J* = 4.5 Hz, 1H), 4.61 (d, *J* = 2.7 Hz, 1H), 4.54 (d, *J* = 3.2 Hz, 1H), 3.80 (s, 3H), 3.73 (s, 3H), 3.03 (d, *J* = 6.2 Hz, 1H), 2.81 (d, *J* = 6.6 Hz, 1H), 2.35 (s, 3H), 2.33 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 174.0, 173.7, 154.0, 153.4, 153.2, 152.9, 137.6, 137.3, 135.5, 133.2, 131.1, 131.0, 129.5, 129.4, 129.3, 128.9, 128.9, 128.8, 127.4, 127.3, 123.8, 123.7, 111.0, 110.1, 106.0, 105.9, 73.9, 73.0, 53.0, 52.8, 49.1, 49.0, 21.3, 21.3; **FT-IR (thin film):** 3492, 2924, 1738, 1542, 1513, 1443, 1259, 1100, 1022, 760, 691 cm^{-1}; **HRMS (+ESI)** Calcd for $[M+H]^+$ $C_{21}H_{21}O_4$ 337.1434; found: 337.1437.

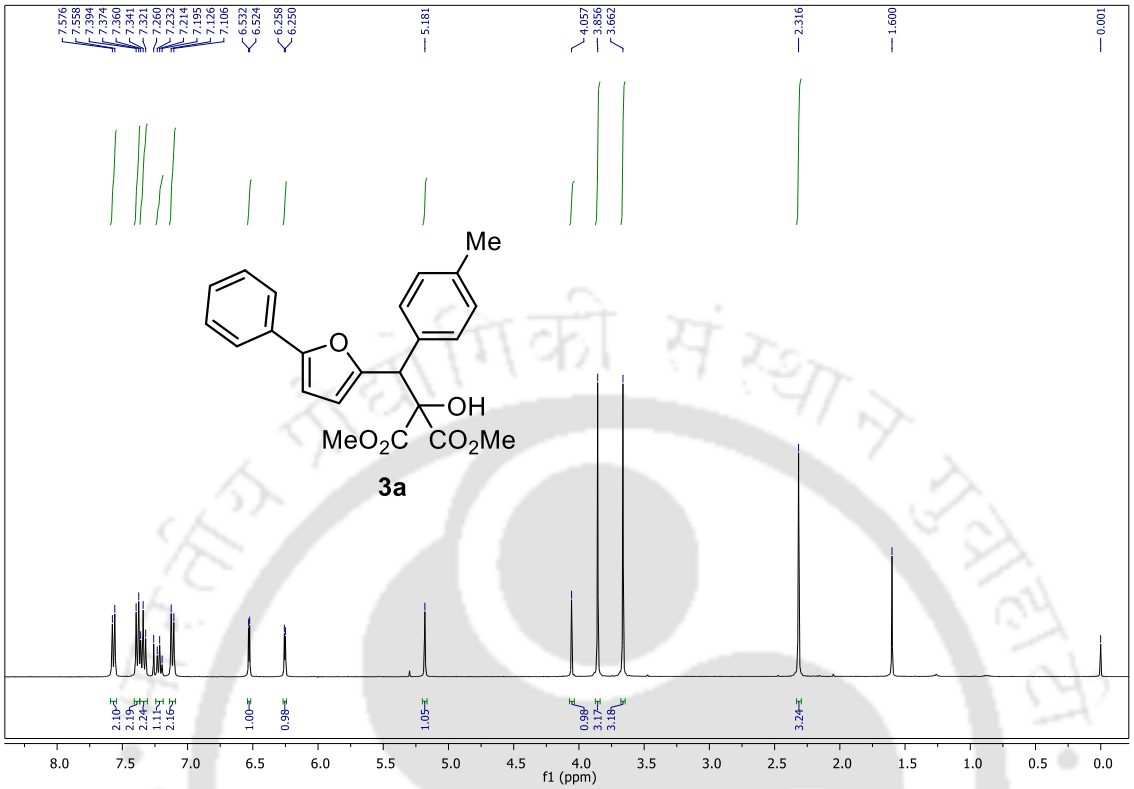
Methyl 3-(5-(4-chlorophenyl)furan-2-yl)-2-hydroxy-3-p-tolylpropanoate (8)

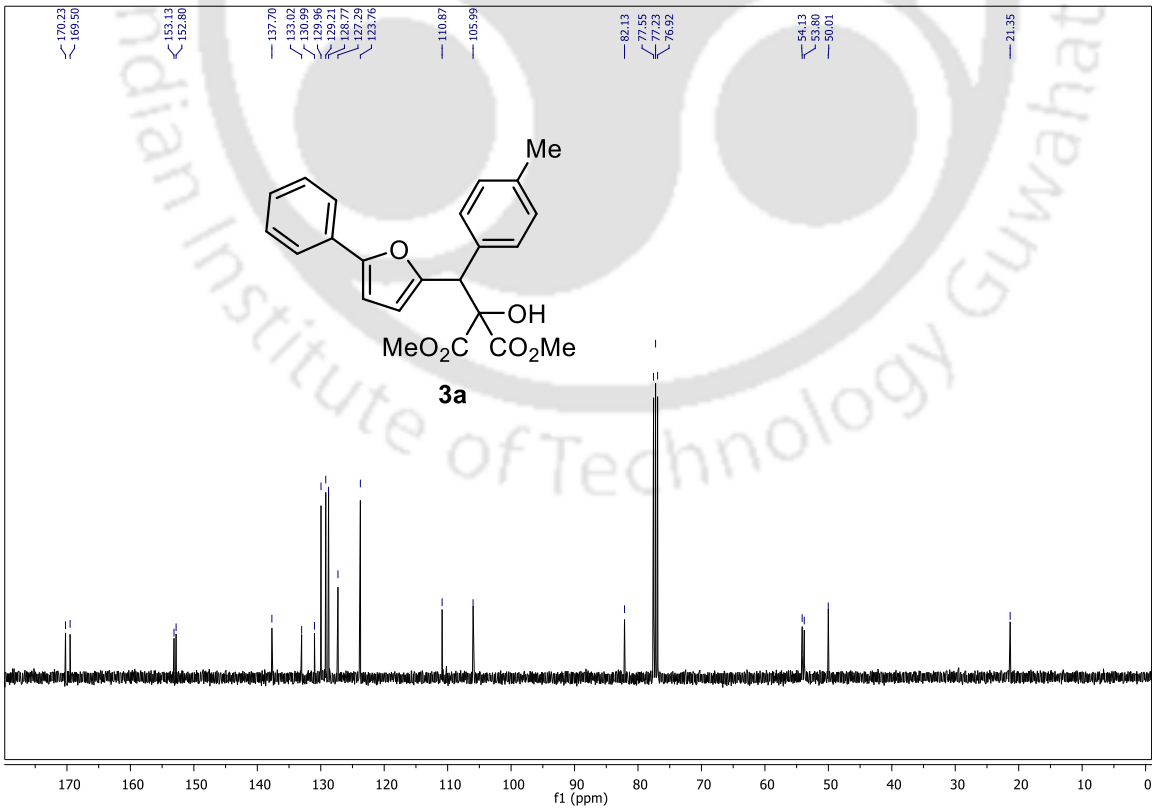


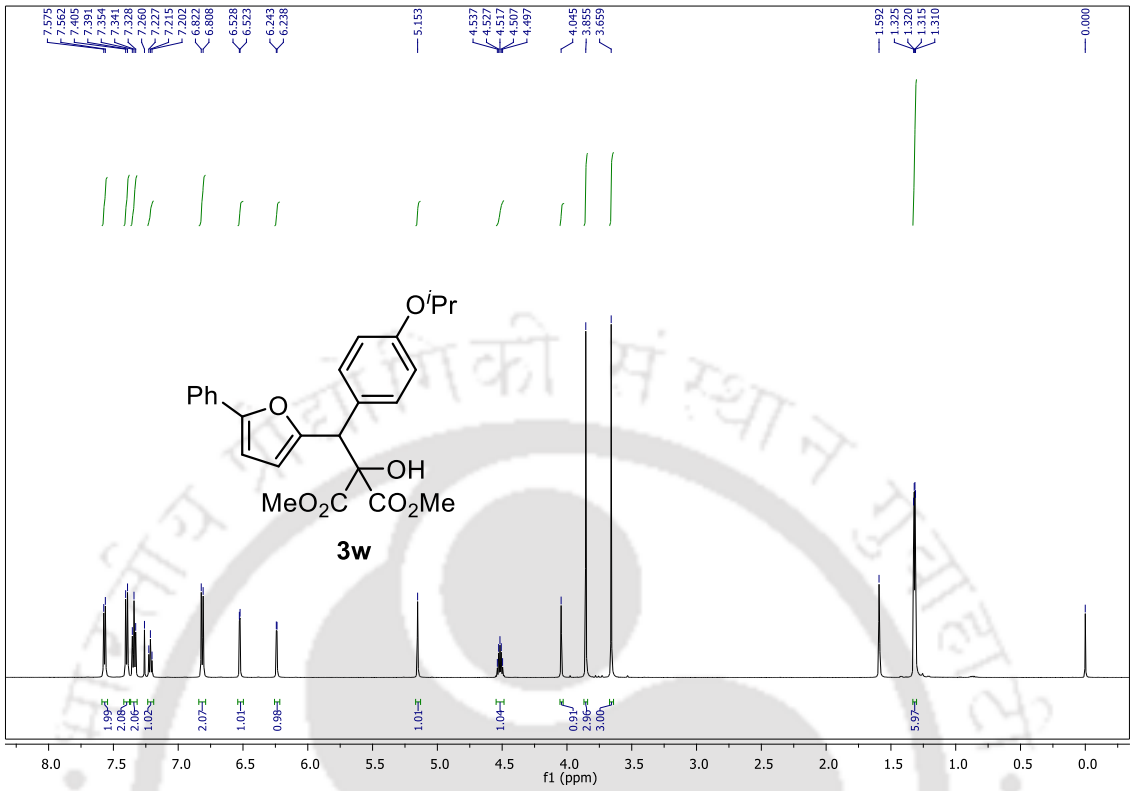
This compound was prepared according to the general procedure E. Reaction was completed after 24 h. Analytical TLC on silica gel using 12% ethyl acetate/hexane. Yellow sticky (24 mg, yield: 64%); **Diastereomeric ratio:** 1:1; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.53 (d, *J* = 8.5 Hz, 2H), 7.50 (d, *J* = 8.5 Hz, 2H), 7.35 – 7.33 (m, 3H), 7.31

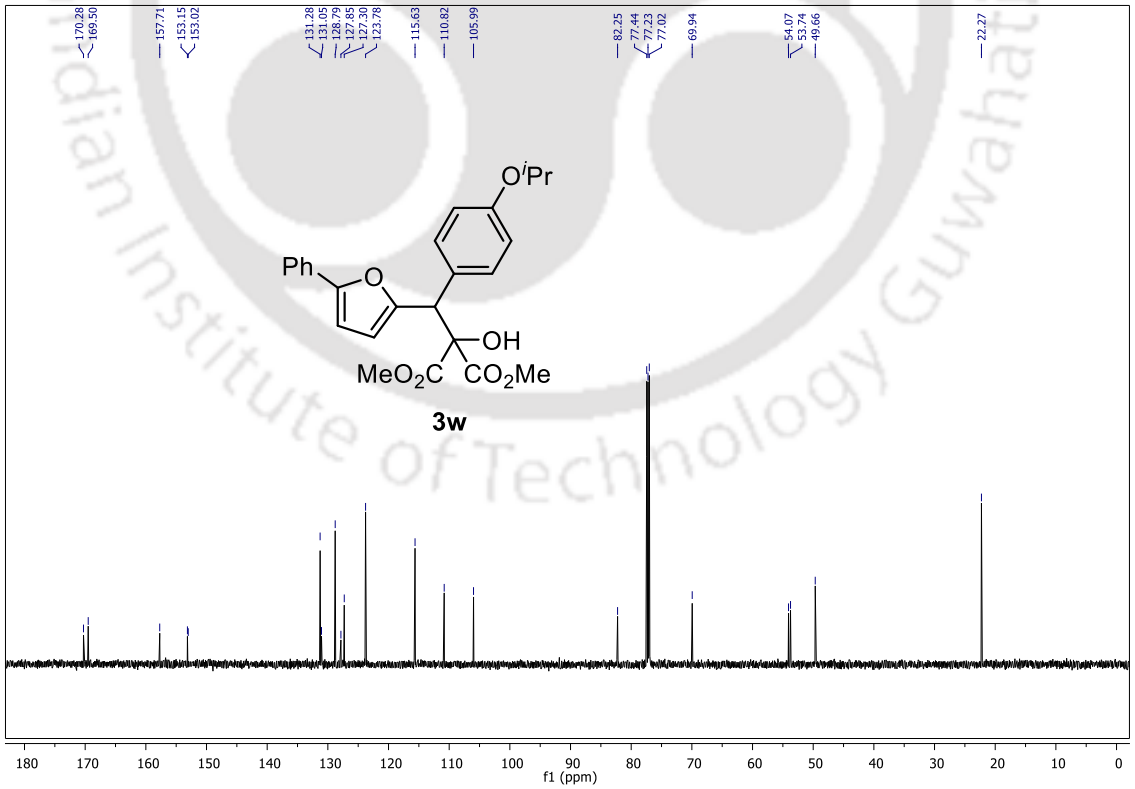
(d, *J* = 8.8 Hz, 3H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.17 (d, *J* = 7.9 Hz, 2H), 7.13 (d, *J* = 7.9 Hz, 2H), 6.57 (d, *J* = 3.3 Hz, 1H), 6.54 (d, *J* = 3.3 Hz, 1H), 6.34 (d, *J* = 3.2 Hz, 1H), 6.19 (d, *J* = 3.3 Hz, 1H), 4.94 (d, *J* = 3.4 Hz, 1H), 4.66 (d, *J* = 3.3 Hz, 1H), 4.58 (d, *J* = 3.5 Hz, 1H), 4.52 (d, *J* = 3.6 Hz, 1H), 3.79 (s, 3H), 3.73 (s, 3H), 2.35 (s, 3H), 2.33 (s, 3H); **^{13}C NMR (75 MHz, CDCl$_3$):** δ 174.0, 173.6, 154.4, 153.4, 152.3, 152.1, 137.7, 137.4, 135.4, 133.0, 132.9, 129.5, 129.4, 129.2, 129.0, 128.9, 128.8, 125.0, 111.0, 110.3, 106.4, 73.8, 72.9, 53.0, 52.8, 49.0, 48.9, 21.3; **FT-IR (thin film):** 3479, 2924, 1739, 1540, 1482, 1094, 827, 785 cm^{-1}; **HRMS (+ESI):** Calcd for $[M+H]^+$ $C_{21}H_{20}ClO_4$ 371.1045; found: 371.1047.

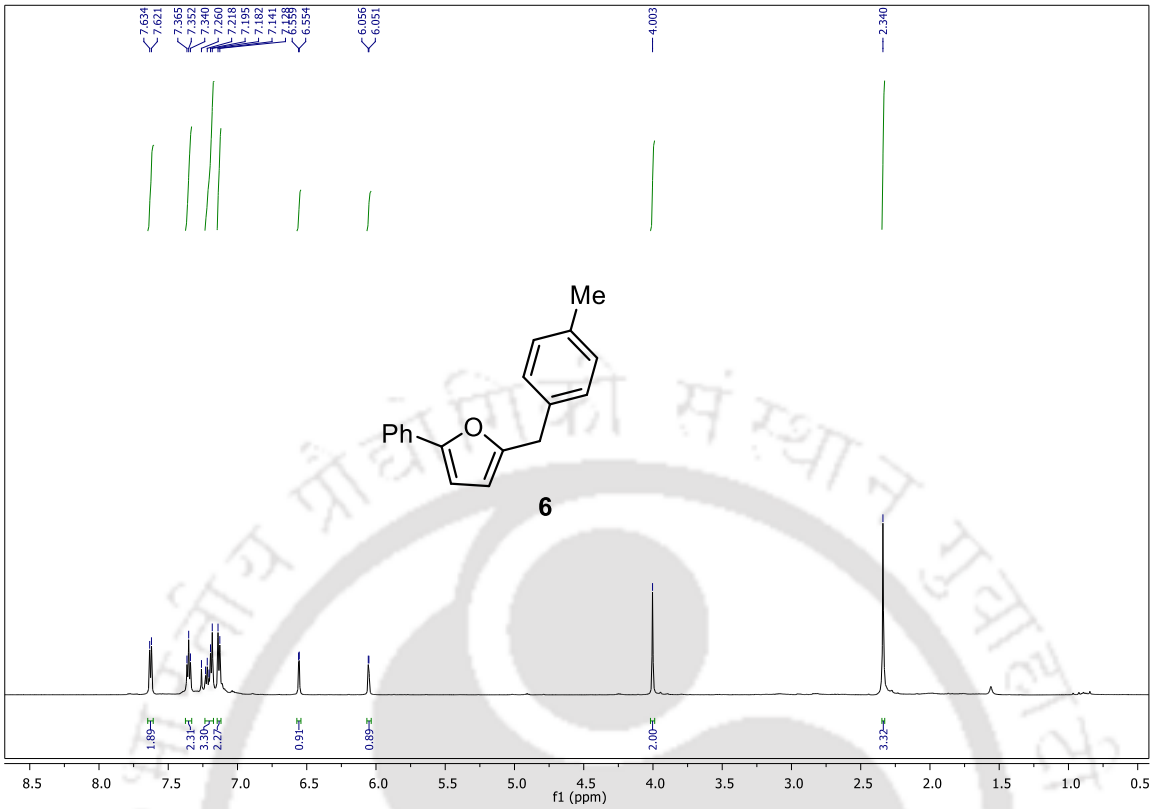
4.9 Selected NMR spectra of products

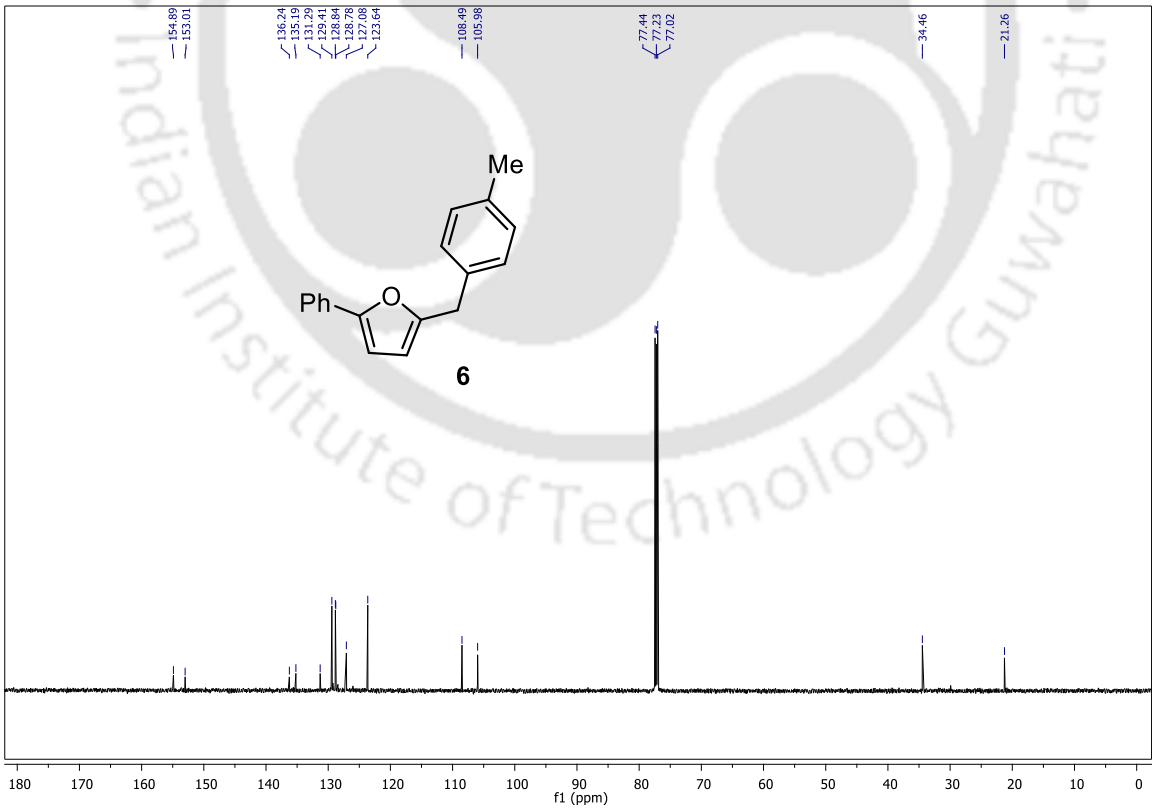












Chapter 5

Organocatalytic Asymmetric Domino Michael/Acyl Transfer Reaction between γ/δ-Hydroxyenones and α-Nitroketones

5.1 Introduction

The conjugate addition of a stabilized carbanion to *α,β*-unsaturated carbonyl compounds is one of the most important C−C bond-forming reactions in organic synthesis.[1] Over the last two decades, organocatalytic asymmetric conjugate additions have established itself as a powerful method for the synthesis of enantiopure organic compounds.[2] The conjugate addition of nitroalkanes and their derivatives to enones is a popular reaction in organic chemistry as the corresponding products can be elaborated to a variety of useful structures such as aminoalkanes, aminocarbonyls and pyrrolidines etc.[3] As a consequence considerable efforts have been put forward for the asymmetric version of this reaction in recent years.[4,5] However, the scope of nitro compounds is limited to nitroalkanes and nitro-esters and surprisingly *α*-nitroketones, another active nucleophiles, have never been applied in the conjugate addition to enones.

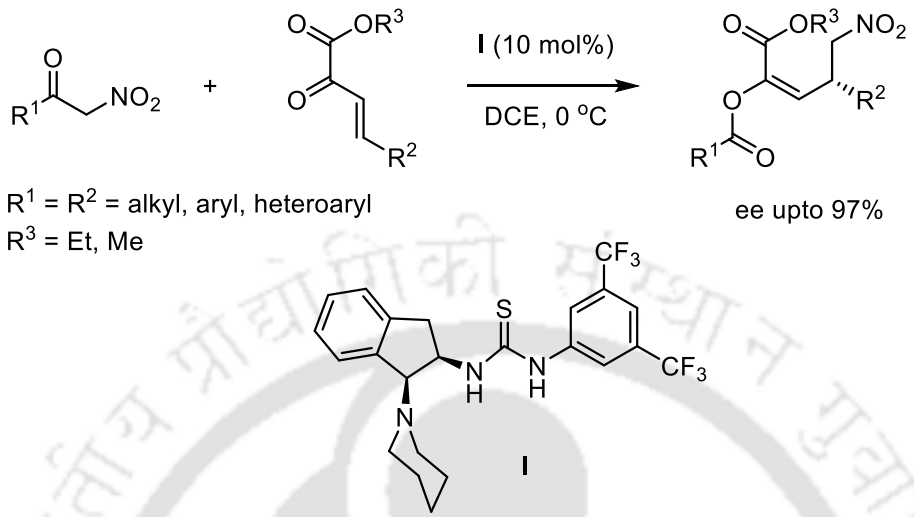
γ/δ-Hydroxyenones are one of the class of bidentate reagents that have been recently exploited in different conjugate addition as well as in many cyclization reactions. Matsubara and co-workers have elegantly developed an intramolecular cyclization of *ω*-hydroxyenones[6] as well as asymmetric synthesis of 1,3-dioxolane, 1,3-oxazolidine and 2-oxazolidinones *via* reactions of *γ*-hydroxyenones with aldehydes, imines and isocyanates respectively.[7]

5.2 Known strategies for Michael and acyl transfer reactions

In the recent past, a variety of methods have been developed for the highly enantioselective Michael addition reactions of nitroalkanes and nitro-esters to *α,β*-unsaturated systems.[4,5] However as an active nucleophilic reagent, *α*-nitroketones were less explored. Previously, few groups independently have disclosed the organocatalytic asymmetric conjugate addition of *α*-nitroketones[8] to *β,γ*-unsaturated *α*-keto esters followed by acyl transfer reaction to the keto group. Interestingly, other electron-deficient carbonyl compounds as well as nitroolefins were found to be unreactive.[9]

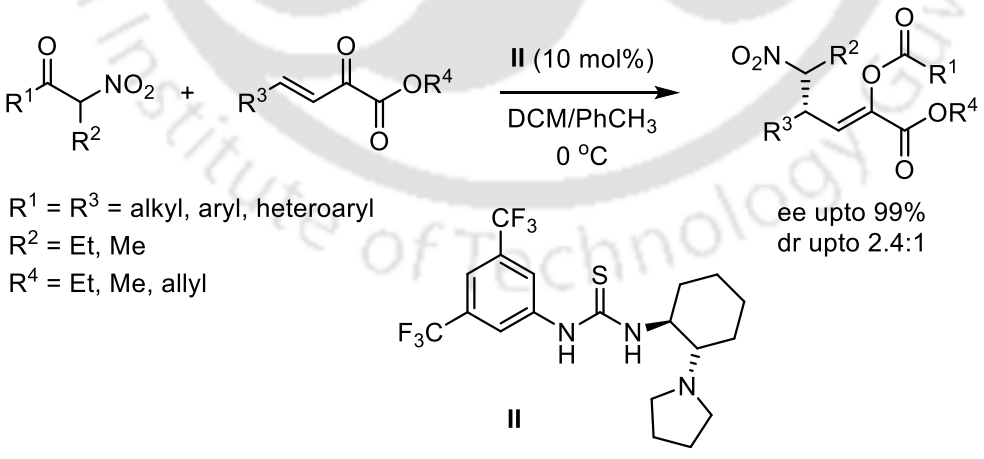
For example, Wang *et al*. reported asymmetric organocatalytic Michael and hemiketalization followed by retro-aldol reaction of *β,γ*-unsaturated ketoesters with *α*-

nitroketones for the synthesis of 5-nitro-pent-2-enoates using bifunctional indane amine-thiourea catalyst **I** (Scheme 5.1).[10]



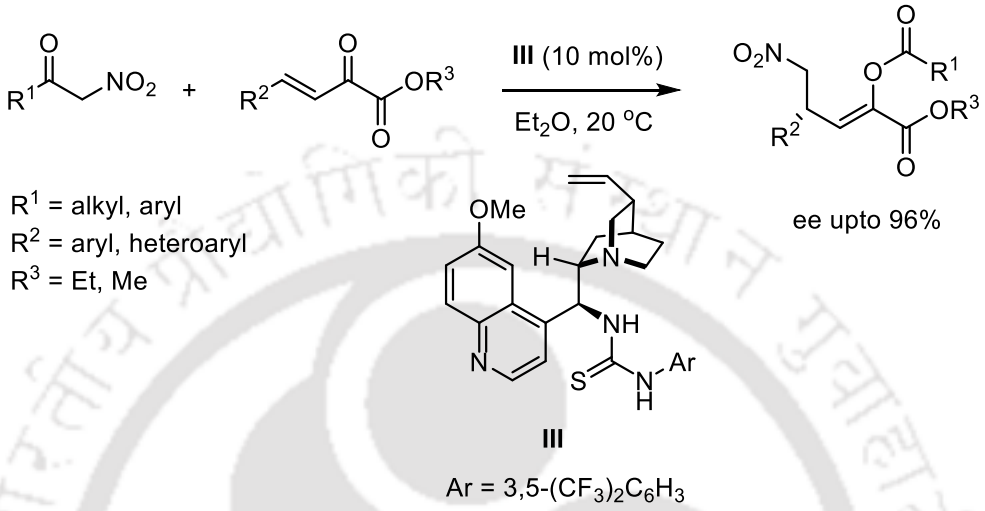
Scheme 5.1: Indane derived thiourea catalyzed asymmetric Michael/acyl transfer reaction

In 2011, the same protocol was performed by Yan and co-workers, varying the catalyst. This research group used cyclohexyl derived tertiary amine thiourea catalyst **II** to obtain the Michael/acyl transfer products with excellent yields and enantioselectivities (Scheme 5.2).[9]



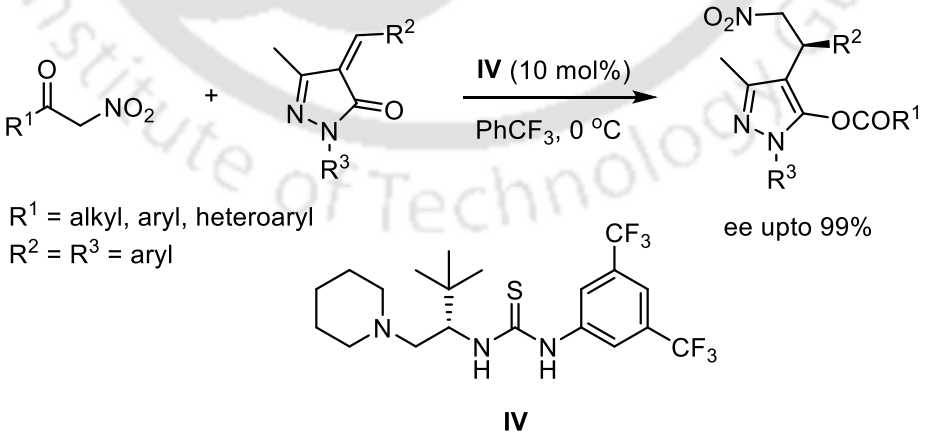
Scheme 5.2: Pyrrolidine based thiourea catalyzed asymmetric Michael/acyl transfer reaction

Later, Kwong group developed cinchona derived thiourea **III** catalyzed reaction of *β,γ*-unsaturated ketoesters with *α*-nitroketones in ether solvent to afford the corresponding products with moderate to good enantioselectivities (Scheme 5.3).[11]



Scheme 5.3: Cinchona derived thiourea catalyzed asymmetric Michael/acyl transfer reaction

More recently, our group demonstrated a new strategy between *α*-nitroketones with unsaturated pyrazolones for the synthesis of highly enantioselective 3-acyloxy pyrazoles *via* Michael/Hemiketalization followed by retro-aldol reaction in the presence of bifunctional thiourea catalyst **IV** (Scheme 5.4).[12]



Scheme 5.4: Organocatalytic asymmetric Michael/Hemiketalization/Retro-aldol reaction

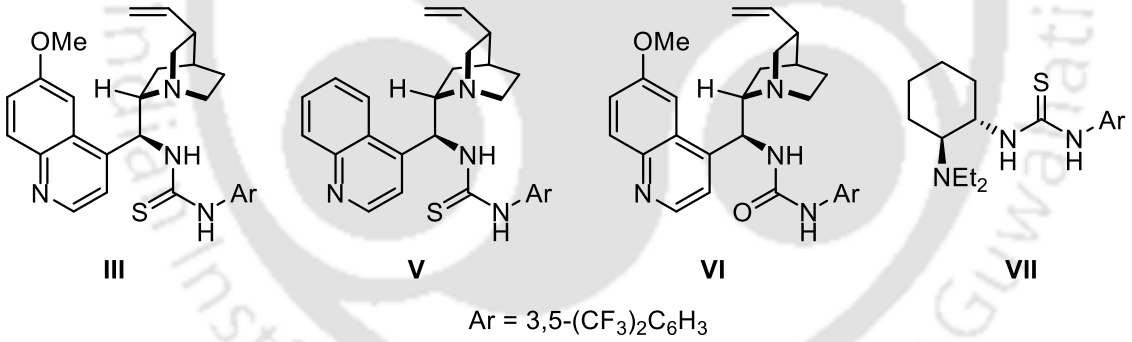
5.3 Result and discussion

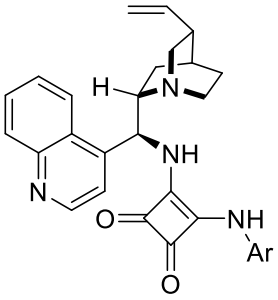
Based on the previously reported literature survey, we found that a reaction between *γ*-hydroxyenones and *α*-nitroketones is still not reported. Realizing the synthetic potential of the nitroketone addition products and our own interest in the acyl transfer reaction,[12] an unprecedented catalytic asymmetric addition of *α*-nitroketones to *γ*/*δ*-hydroxyenones has been highlighted in this chapter.

Initially, the optimization of the reaction was carried out between (*E*)-4-hydroxy-1-phenylbut-2-en-1-one (**1a**) and 2-nitro-1-phenylethanone (**2a)** with quinine derived bifunctional thiourea catalyst **III** in toluene at room temperature (Table 1). Gratifyingly, after stirring for 2 days, the desired product was isolated with 65% yield and moderate (62%) enantioselectivity (Table 1, entry 1). The product was identified as **3a** which was formed *via* conjugate addition followed by benzoyl transfer reaction.

Optimization of reaction condition

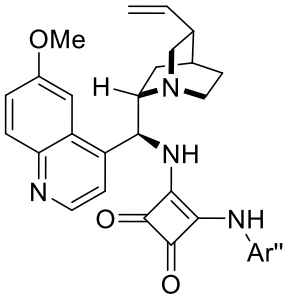
Table 1: Catalyst screening





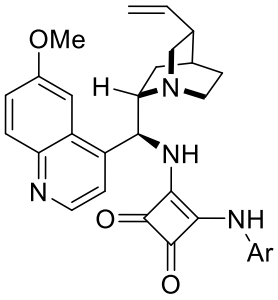
XI

Ar = 3,5-$(CF_3)_2C_6H_3$



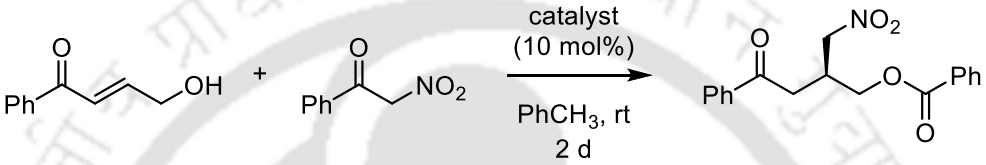
XII

Ar'' = 4-$CF_3C_6H_4$



XIII

Ar = 3,5-$(CF_3)_2C_6H_3$



1a + **2a** → **3a**

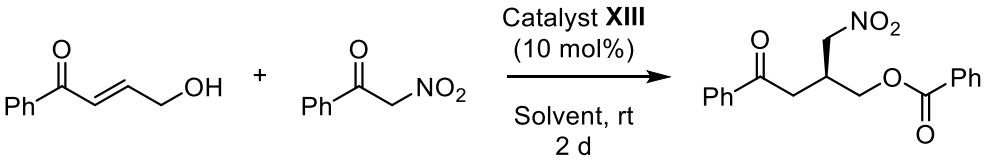
entry[a]	catalyst	yield (%)[b]	ee (%)[c]
1	**III**	65	62
2	**V**	63	72
3	**VI**	62	70
4	**VII**	58	68
5	**VIII**	65	84
6	**IX**	70	84
7	**X**	73	94
8	**XI**	80	94
9	**XII**	90	94
10	**XIII**	93	96

[a]Reaction conditions: 0.1 mmol of **1a** with 0.12 mmol of **2a** in 0.5 mL solvent using 10 mol% catalyst. [b]Isolated yield after silica gel column chromatography. [c]Determined by HPLC.

In order to improve the enantioselectivity, a variety of organocatalysts were screened under the reaction condition. The enantioselectivity was slightly improved using cinchonidine derived thiourea **V** and quinine derived urea **VI** catalysts (Table 1, entries 2-3). The outcome was not much different with cyclohexyl derived thiourea catalyst **VII**, providing moderate yield and enantioselectivity, with opposite enantiomer (Table 1, entry 4). Then, the investigation was switched to screen different bifunctional squaramide catalysts[13] and the results were pleasing for us. For example, the enantioselectivity got improved to 84% ee using catalyst **VIII** (Table 1, entry 5). In contrast, similar enantioselectivity was observed for catalyst **IX** (Table 1, entry 6). Then catalyst **X** having 4-CF_3 moiety was employed in the reaction and both the yield as well as enantioselectivity got enhanced (Table 1, entry 7). Comparable enantioselectivity with slight improvement in yield was attained using catalyst **XI** (Table 1, entry 8). The yield was further improved to 90% with quinine derived squaramide catalyst **XII** having 4-CF_3 moiety (Table 1, entry 9). Finally, the best catalyst was turned out to be quinine derived squaramide catalyst **XIII** which provided product **3a** with 93% yield and 96% ee (Table 1, entry, entry 10).

With the best catalyst in hand, next solvent and temperature effects on the reaction were studied (Table 2). Interestingly, the outcome did not alter for enantioselectivity. Halogenated solvents such as DCM, DCE, and $CHCl_3$ were screened and similar enantiomeric excess as in toluene was detected (Table 2, entries 1-3). Smooth conversion was also observed in ether solvent like MTBE providing 90% yield and 96% ee (Table 2, entry 4). $PhCF_3$ solvent also afforded the product **3a** with 81% yield and 94% enantioselectivity under the reaction condition (Table 2, entry 5). Finally, catalyst **XIII** in $PhCH_3$ solvent was found to be the best condition in terms of yield and enantioselectivity (Table 2, entry 6). When the reaction was carried out at 0 ^oC in toluene, the enantioselectivity was remained same but the yield got reduced substantially (Table 2, entry 7). Decreasing the concentration of the reaction, slightly lower yield was observed maintaining the same enantioselectivity (Table 2, entry 8).

Table 2: Solvent screening



1a **2a** **3a**

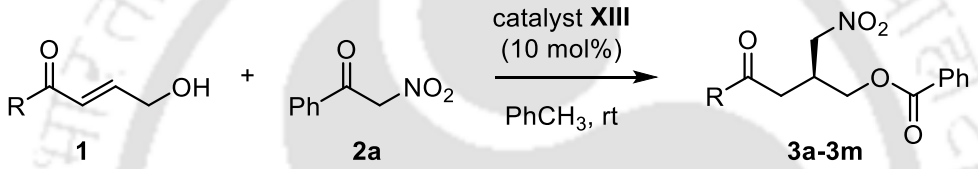
entry[a]	solvent	yield (%)[b]	ee (%)[c]
1	DCM	86	96
2	DCE	83	96
3	$CHCl_3$	82	96
4	MTBE	88	96
5	$PhCF_3$	81	94
6	$PhCH_3$	93	96
7[d]	$PhCH_3$	56	96
8[e]	$PhCH_3$	89	96

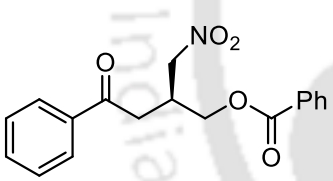
[a]Reaction conditions: 0.1 mmol of **1a** with 0.12 mmol of **2a** in 0.5 mL solvent using 10 mol% catalyst. [b]Isolated yield after silica gel column chromatography. [c]Determined by HPLC. [d]Reaction was performed at 0 °C. [e]Using 0.1[M] conc.

5.4 Substrate scope

After identifying the best catalyst and the optimized reaction conditions, the scope and generality of the reaction was investigated. Initially, different γ-hydroxyenones having a variety of substitutions on the aryl group were prepared and engaged in the reaction (Scheme 5.5). Gratifyingly, as can be seen, excellent enantioselectivities (>90% ee) were achieved for all cases. For example, enones **1b** having 4-methyl group delivered product **3b** with 76% yield and 96% ee. 4-*tert*-butyl enone **1c** provided the product **3c** with 63% yield and similar enantiomeric excess. Interestingly, the reaction was slower for enone **1d** and reasonable yield was achieved only after 5 days and product **3d** was isolated in an excellent enantiomeric excess. Then, enones **1e-1g** having 4-halosubstituted aryl groups

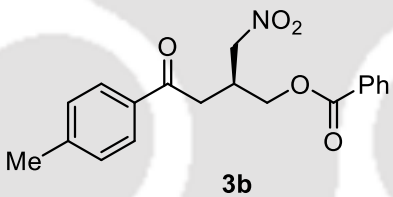
were subjected to the reaction conditions. To our delight, the desired products **3e-3g** were isolated in acceptable yields after 3 days and excellent enantiomeric excesses were detected. 4-fluoro substituted enone **1e** produced the product **3e** with 72% yield and 94% ee. Other 4-halosubstituted enones executed similar enantioselectivities for their products. Then, different *m*-substituted aryl enones were screend under the reaction conditions. Interestingly, smooth conversions were observed for 3-methyl and 3-methoxy enones delivering the products **3h** and **3i** with high enantioselectivities (Scheme 5.5). The reaction outcome also did not change with *o*-substituted aryl enone **1j** and product **3j** was obtained with 92% enantiomeric excess. However, enone **1k** having 1-naphthyl group also participated well in the reaction providing excellent results after longer reaction time.





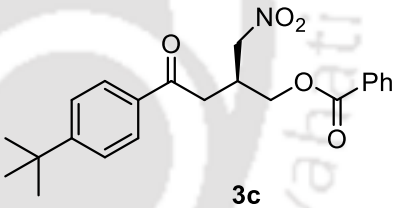
3a

2 d, 93%, 96% ee



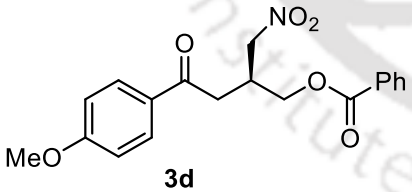
3b

3 d, 76%, 96% ee



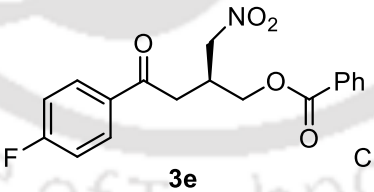
3c

3 d, 63%, 96% ee



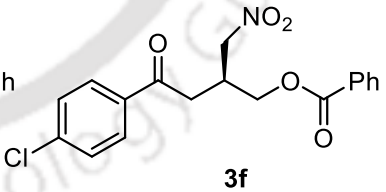
3d

5 d, 53%, 96% ee



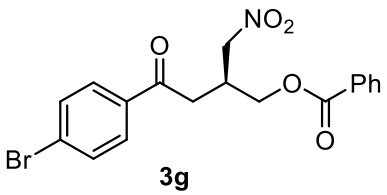
3e

3 d, 72%, 94% ee



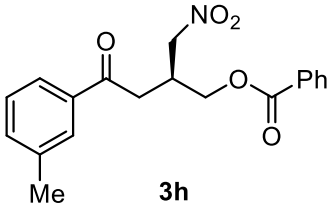
3f

3 d, 75%, 94% ee



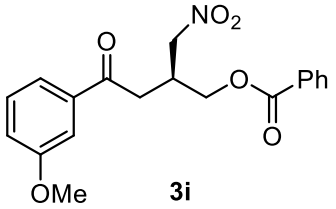
3g

3 d, 84%, 94% ee



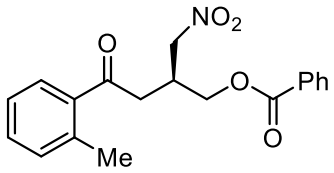
3h

3 d, 76%, 92% ee



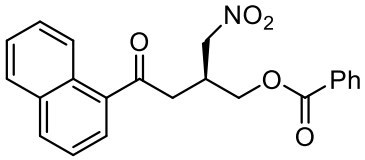
3i

3 d, 61%, 96% ee



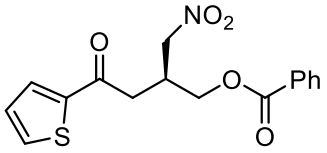
3j

3 d, 64%, 92% ee



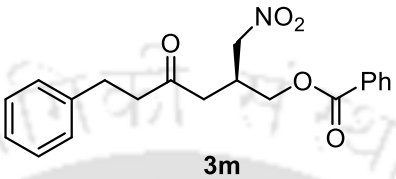
3k

5 d, 58%, 91% ee



3l

4 d, 72%, 92% ee



3m

3 d, 51%, 62% ee[d]

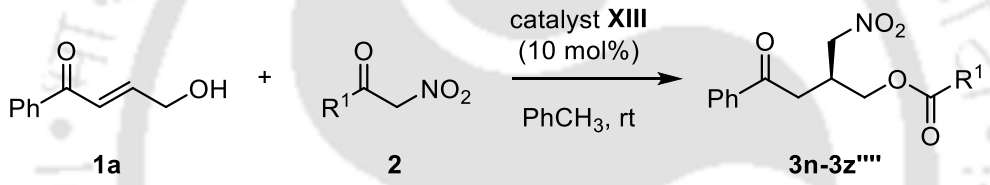
[a]Reaction conditions: 0.1 mmol of **1** and 0.12 mmol of **2a** in 0.5 mL $PhCH_3$ using 10 mol% catalyst. [b]Isolated yield after silica gel column chromatography. [c]Determined by HPLC. [d]Reaction was performed at 45 °C.

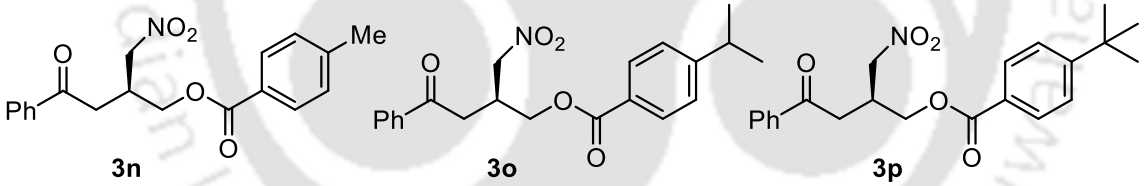
Scheme 5.5: Scope of γ-hydroxyenones in the Michael/acyl transfer reaction[a,b,c]

In addition, heteroaromatic enone **1l** was tested in the reaction and high enantioselectivity was observed for product **3l**. Finally, aliphatic enone **1m** having hydrocinamyl moiety was prepared and engaged in the standard reaction conditions. However, a trace amount of product was osberved after 4 days at room temperature. Then, the reaction was placed at 45 °C for 3 days, furnishing the product **3m** with 51% of yield but the enantiomeric excess was dropped significantly.

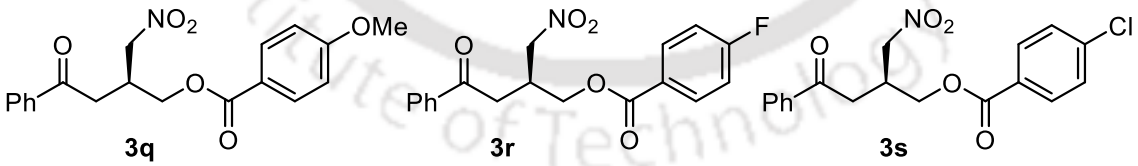
After that, the scope of the nitroketones was studied and pleasingly a variety of groups including aliphatic functionalities were tolerated and excellent results (>90% ee) were achieved (Scheme 5.6). A range of substitutions were incorporated at the *ortho, para* and *meta* positions on the phenyl ring of α-nitroketones irrespective of their electronic nature. Different 4-alkyl and 4-alkoxy substituted aryl nitroketones **2b**-**2e** were screened under the reaction conditions. The yield and enantioselectivity of the corresponding products **3n**-**3q** were found to be similar as observed for unsubstituted nitroketone product **3a**. Then 4-halosubstituted nitroketones **2f**-**2h** were tested in the reaction, furnishing the products **3r**-**3t** with good yields and enantioselectivities.

For 4-halosubstituted nitroketones the enantioselectivities diminished in a sequence of Br>Cl>F. It was found that the reaction was slightly slower for electron-withdrawing group compared to electron-donating group present in the aryl nitroketones. The substitution at the *ortho* and *meta* positions of the aryl ring did not influence considerably on the enantioselectivity. For example, 3-methyl nitroketone **2i** afforded the Michael/acyl transfer product **3u** with high yield and enantioselectivity. In particular, an excellent 98% ee was achieved for product **3v** having 3-methoxy substitution. Moderate yield with high enantiomeric excess of the product **3w** was attained for 3-chloro substituted nitroketone. This methodology was also suitable for *o*-substituted nitroketones and comparable yields along with enantioselectivities were observed for 2-methyl (**3x**) and 2-fluoro (**3y**) substituted products. 2,4-Disubstituted aryl nitroketone **2n** was also engaged in the reaction and the desired product **3z** was obtained with 93% ee.

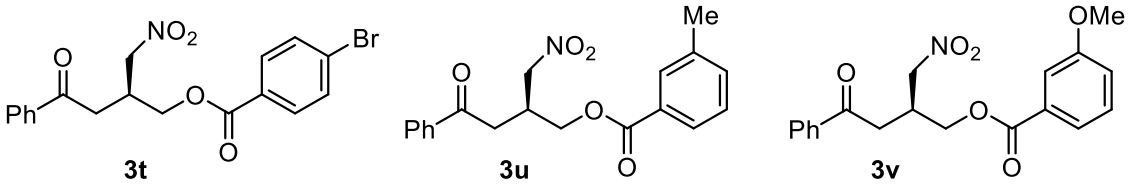




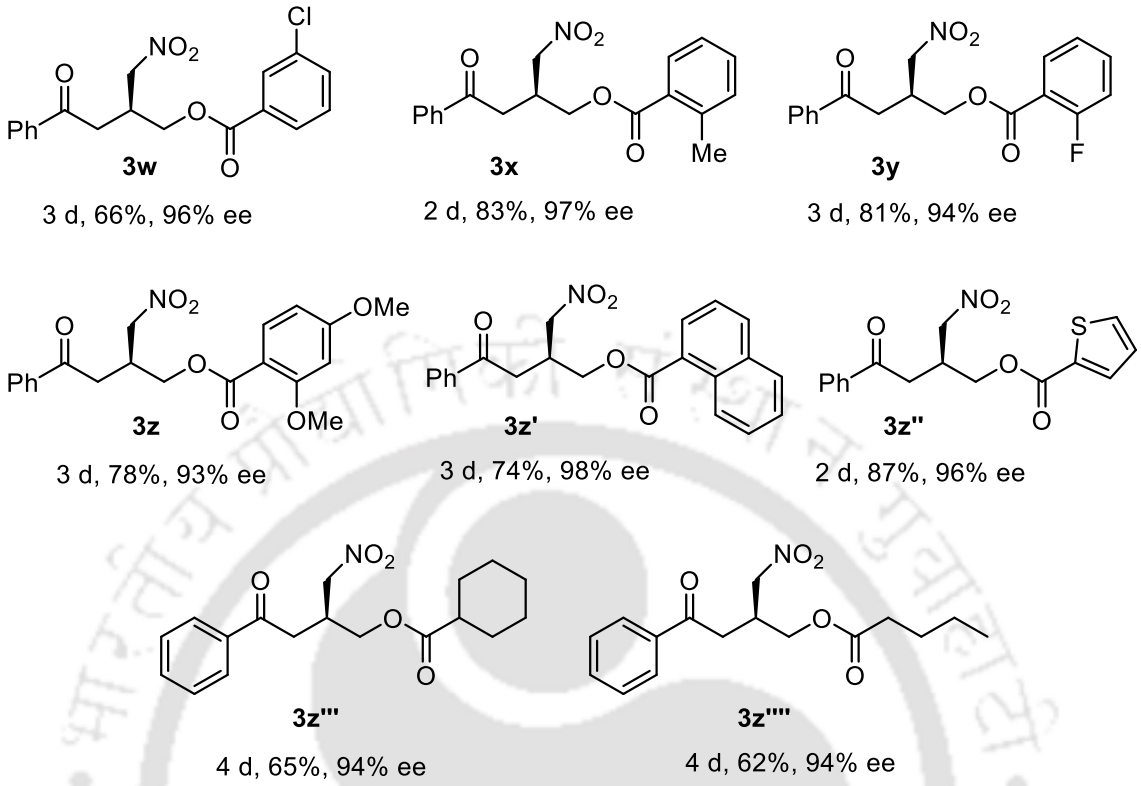
2 d, 85%, 96% ee | 2 d, 90%, 94% ee | 2 d, 83%, 94% ee



2 d, 91%, 96% ee | 3 d, 82%, 90% ee | 3 d, 81%, 95% ee



3 d, 78%, 96% ee | 2 d, 82%, 92% ee | 2 d, 86%, 98% ee



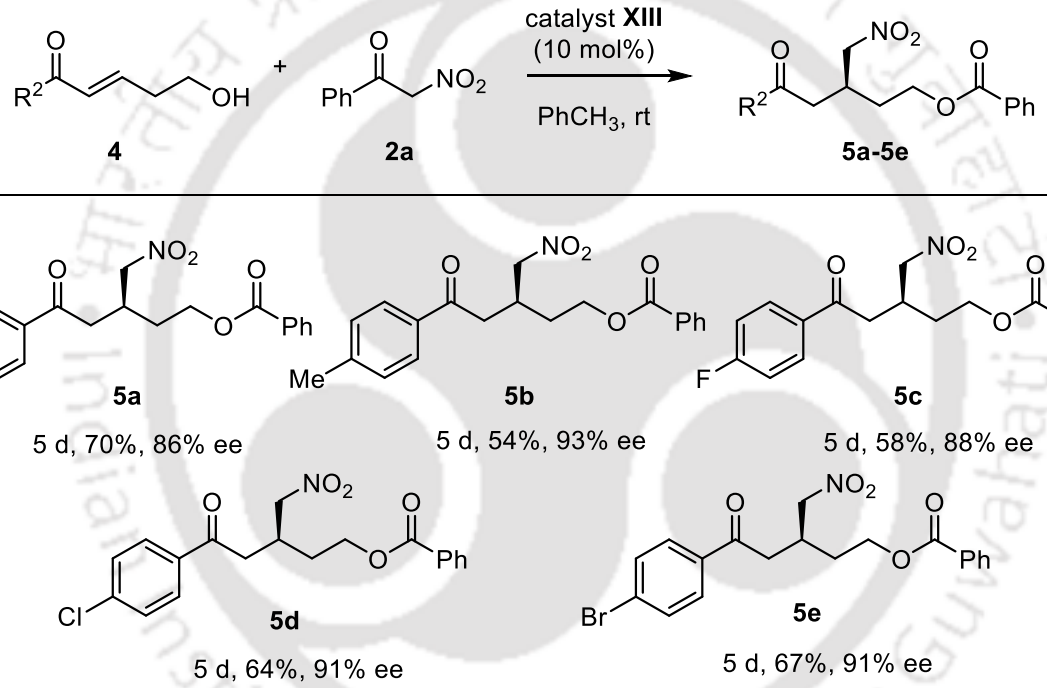
[a]Reaction conditions: 0.1 mmol of **1a** and 0.12 mmol of **2** in 0.5 mL $PhCH_3$ using 10 mol% catalyst. [b]Isolated yield after silica gel column chromatography. [c]Determined by HPLC.

Scheme 5.6: Scope of nitroketones in the Michael/acyl transfer reaction with **1a**[a,b,c]

The reaction also progressed well for nitroketone **2o** having 1-naphthyl motif under the reaction and 98% ee was detected for product **3z′**. In contrast, Smooth conversion was observed with heteroaromatic nitroketone **2p** delivering the product **3z′′**. Finally aliphatic nitroketones **2q** and **2r** were prepared and engaged in the reaction. To our delight, the desired products **3z'''** and **3z''''** were isolated with acceptable yields and high enantioselectivities after 4 days.

The generality of the reaction was further extended by engaging different *δ*-hydroxyenones in the reaction (Scheme 5.7). Interestingly, under the same reaction conditions, (*E*)-6-hydroxy-1-phenylhex-2-en-1-one (**4a**) on reaction with nitroketone **2a** delivered the desired product **5a** with 70% yield and 86% ee *albeit* the reaction time was 5 days. Then different 4-substituted aryl group containing *δ*-hydroxyenones were

prepared and employed in the reaction. Pleasingly, the corresponding products **5b**-**5e** were obtained in acceptable yields and with high enantioselectivities. 4-methyl substituted *δ*-hydroxyenones (**4b**) was subjected to the reaction conditions, delivering the product **5b** with a moderate yield and slight increase in enantioselectivity was observed compared to **5a**. In addition, different 4-halosubstituted enones were introduced and similar enantiomeric excess were obtained for the products **5d** and **5e** bearing 4-chloro and 4-bromo moieties. Noteworthy, a little bit decrease in enantioselectivity was observed for 4-fluoro substituted product **5c** compared to other 4-halosubstituted products.

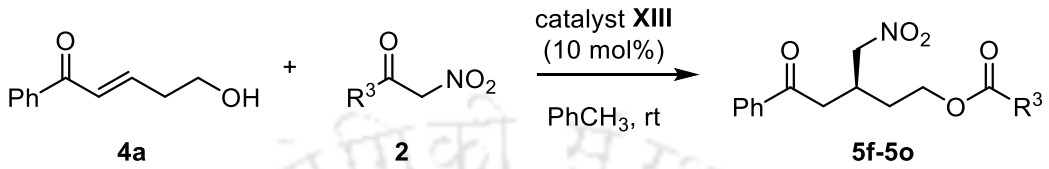


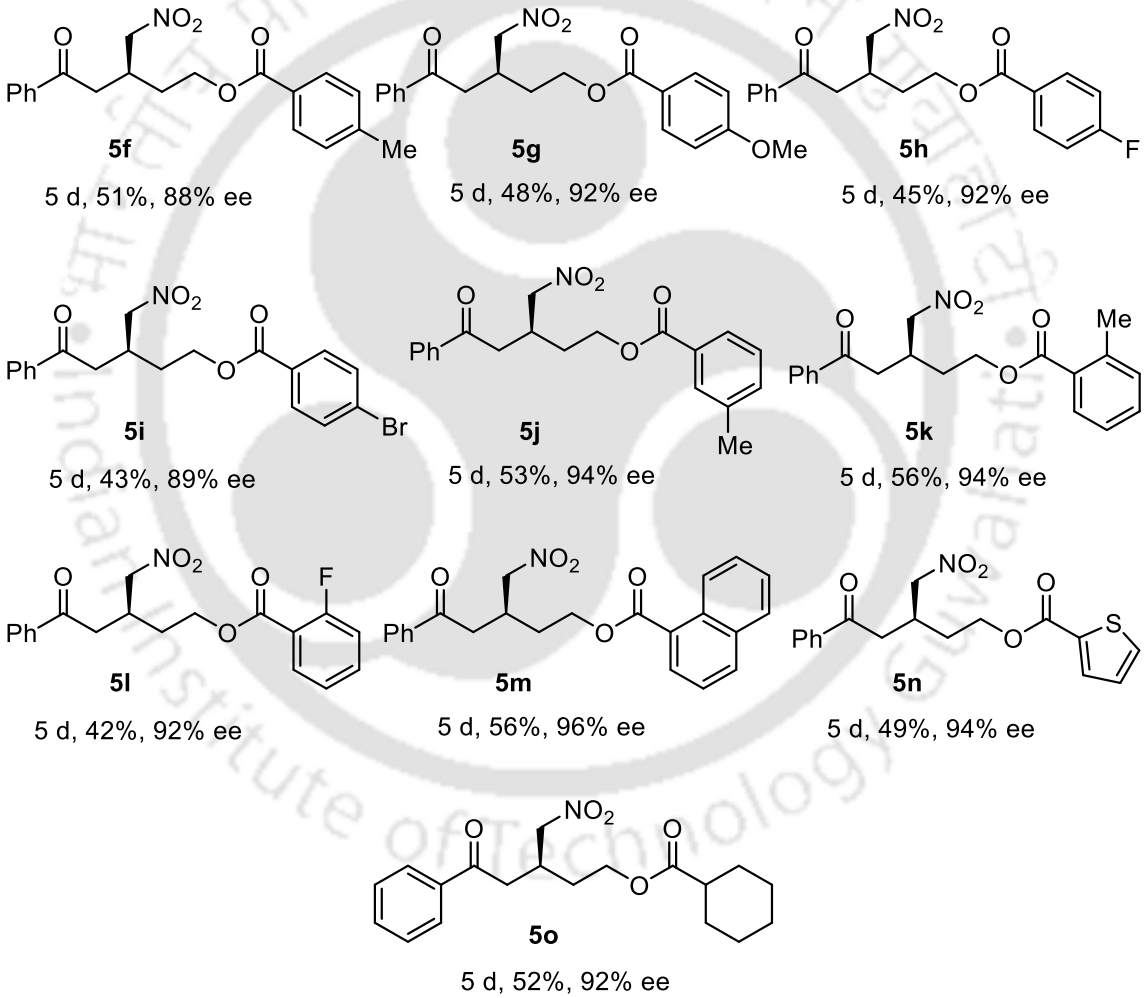
[a]Reaction conditions: 0.1 mmol of **4** and 0.12 mmol of **2a** in 0.5 mL $PhCH_3$ using 10 mol% catalyst. [b]Isolated yield after silica gel column chromatography. [c]Determined by HPLC.

Scheme 5.7: Scope of *δ*-hydroxyenones in the Michael/acyl transfer reaction[a,b,c]

To further lengthen the scope of the reaction, (*E*)-6-hydroxy-1-phenylhex-2-en-1-one (**4a**) was treated with a variety of nitroketones **2** (Scheme 5.8). Here also, high enantioselectivities were achieved irrespective of the electronic nature of the aryl group of the nitroketones. Initially, different 4-substituted aryl nitroketones were examined, and the corresponding products **5f**-**5i** were isolated in moderate yields with high

enantioselectivities. For example, 4-methyl and 4-methoxy nitroketones supplied the products **5f** and **5g** with good enantiomeric excess. Similar results were observed for 4-halosubstituted nitroketones **2f** and **2h** affording the products **5h** and **5i**. *Meta*-substituted nitroketone **2i** also took part in the reaction and delivered the product **5j** in 94% ee.



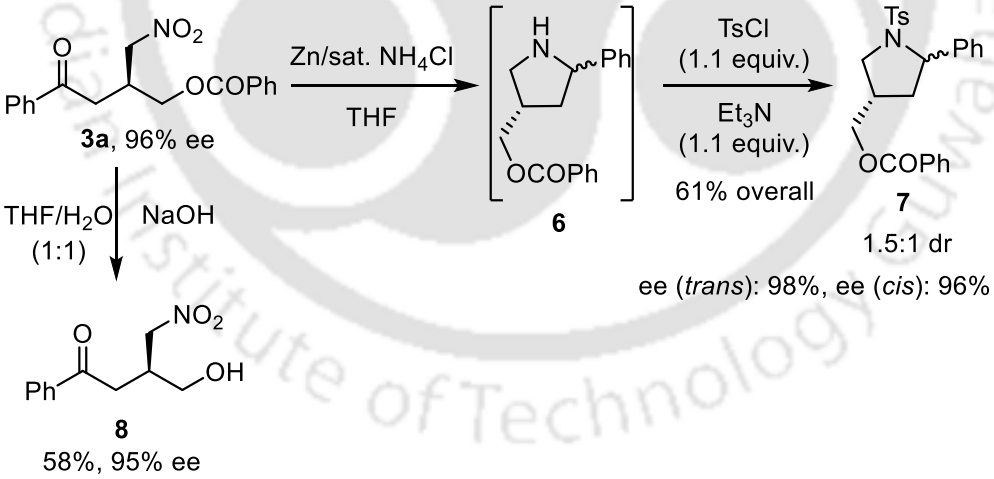


[a]Reaction conditions: 0.1 mmol of **4a** and 0.12 mmol of **2** in 0.5 mL $PhCH_3$ using 10 mol% catalyst. [b]Isolated yield after silica gel column chromatography. [c]Determined by HPLC.

Scheme 5.8: Scope of nitroketones in the Michael/acyl transfer reaction with **4a**[a,b,c]

Additionally, moderate yield and high enantioselectivity were observed for the products **5k** and **5l** having *o*-substituents in aryl ring. 1-Naphthyl containing nitroketone also underwent the reaction with **4a** leading to the formation of the product **5m** with excellent enantioselectivity (96%). Gratifyingly, heteroaromatic nitroketone **2p** having thiophene motif was also able to endure the reaction conditions giving the Michael/acyl transfer product **5n** with 94% ee. Finally, aliphatic nitroketone **2q** was engaged in the reaction and delivered the product **5o** with decent yield and high enantiomeric excess. From these experiments, it was concluded that γ-hydroxyenones produced superior results compared to δ-hydroxyenones, possibly due to the ease of formation of five membered hemiketal intermediates (Scheme 5.11).

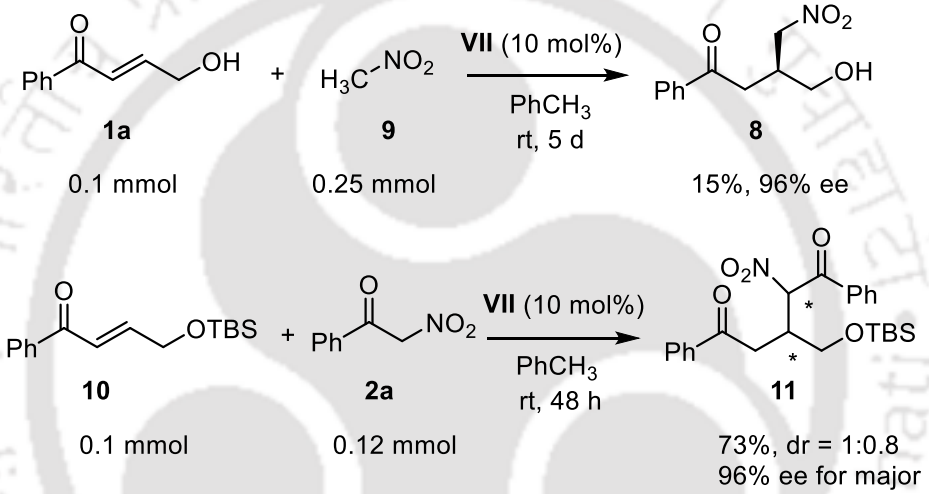
To illustrate the synthetic utility of our methodology, few reactions were carried out on **3a** (Scheme 5.9). Initially, reductive amination reaction was performed on **3a** with Zn/NH_4Cl and thus pyrrolidine **6** was formed.[14] The pyrrolidine **6**, without purification, was converted to **7** using TsCl and triethylamine. The diastereomeric ratio for **7** was found to be 1.5:1 and the enantiopurity for the major *trans*-isomer was 98% ee whereas the enantiomeric excess of the minor *cis*-isomer was 96%.



Scheme 5.9: Synthetic transformation of **3a**

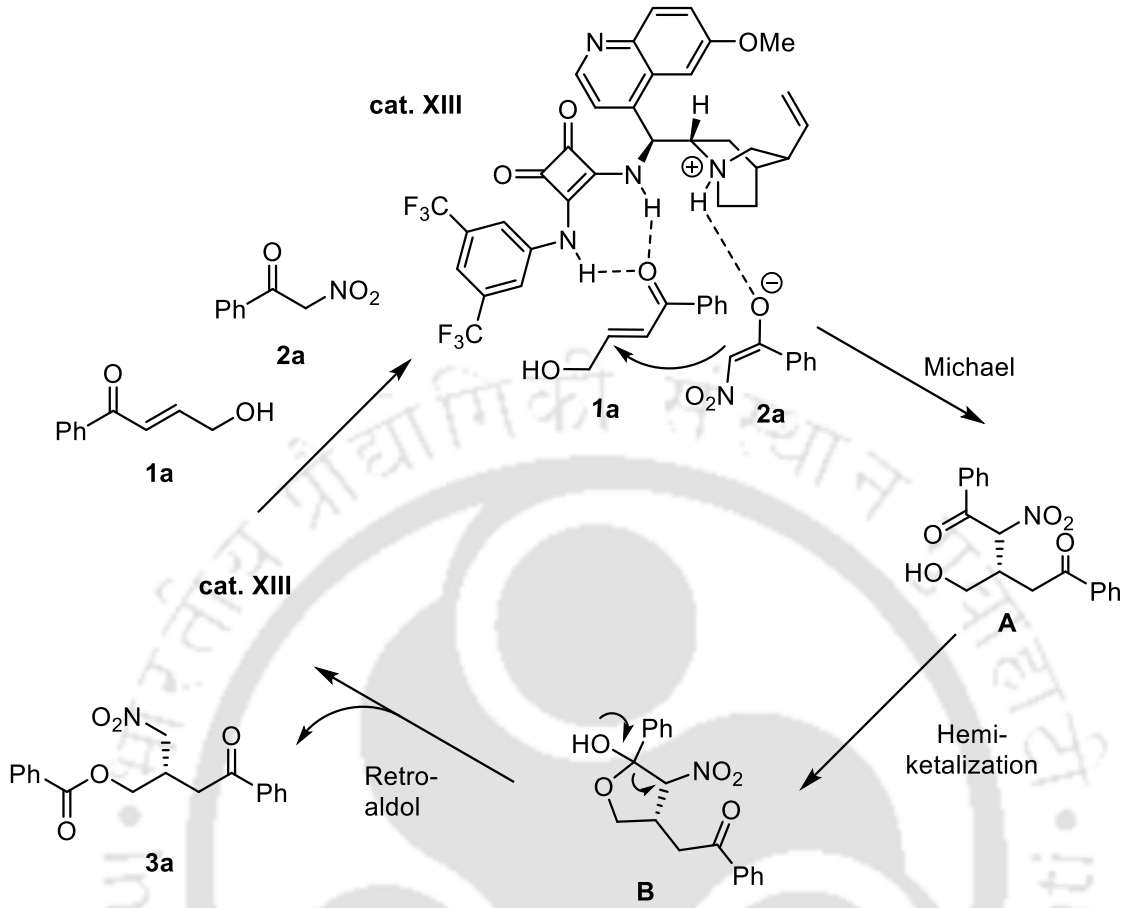
The relative stereochemistry of the product **7** was determinded by 2D NMR (NOESY, COSY and HSQC) analysis. Then, **3a** was treated with sodium hydroxide to hydrolyze the ester group and this led to the formation of alcohol **8** with good yield and almost preservation of enantiopurity (Scheme 5.9).

Interestingly, the reaction between nitromethane (**9**) and **1a** was very slow though the enantioselectivity for the corresponding product **8** was high (Scheme 5.10). An experiment has also been performed using TBS protected enone (**10**) and *α*-nitroketone (**2a**) in the presence of catalyst **VII** and the single Michael addition product was formed in 73% yield with 1:0.8 diastreomeric ratio having 96% ee for the major diastereomer. From these experiments, it can be concluded that Michael addition step (1st step) is the stereocontrol step in our reaction. The rate determining step also will be the Michael step as we do not observe any intermediate even running the reaction at lower temperature.



Scheme 5.10: Control experiments

The absolute configuration of **3g** was solved by X-ray crystallography and was found to be (*S*).[15] Thus, other products **3** and **5** were assumed to have the same absolute structure by analogy. Based on the literature study and absolute structure (confirmed by X-ray crystallography), a plausible mechanism has been depicted in Scheme 5.11. This indictates a bifunctional mode of activation of both the reactants by catalyst **XIII**, the quinuclidine motif activates nitroketone **2a** and simultaneously squaramide moiety binds with the carbonyl group of enone **1a**. Thus, the *Si* face of the olefin is blocked by the catalyst and conjugate addition takes place from the *Re* face to provide intermediate **A**. Then, the intermediate **B** was formed *via* hemiketalization from intermediate **A**. Finally, retro-aldol reaction of intermediate **B** delivered the desired product **3a**.



Scheme 5.11: Plausible mechanism for the formation of **3a**

In conclusion, a novel organocatalytic Michael reaction of *α*- nitroketones to *γ/δ*-hydroxyenones has been described in this chapter. The reaction proceeds through conjugate addition and consequent acyl transfer to deliver a range of 2-(nitromethyl)-4-oxo-4-arylbutyl benzoates and 3-(nitromethyl)-5-oxo-5-arylpentyl benzoates with high yields and excellent enantioselectivities. Also, the usefulness of our methodology was shown *via* few synthetic transformations including a synthesis of 2,4-disubstituted pyrrolidine. Future developments of related Michael acyl transfer reactions are in progress in our laboratory.

5.5 Experimental section

General Information

All commercial reagents were purchased with the highest purity grade. They were used without further purification unless specified. All reactions were carried out in oven dried glassware with magnetic stirring. Dichloromethane was distilled over CaH_2 under argon and stored over 4Å molecular sieves. All other solvents and reagents were purified according to standard procedures. Organic solvents were dried over anhydrous Na_2SO_4 and concentrated in a rotary evaporator under reduced pressure. Reactions were monitored by TLC on silica gel GF-254 using a combination of hexane and ethyl acetate as eluents. For column chromatography silica gel (60-120 mesh size) was used.

^{1}H NMR spectra were recorded on a 400 MHz, 500 MHz and 600 MHz spectrometer at 295 K in $CDCl_3$; chemical shift values (δ, ppm) were reported in the standard fashion with reference to either tetramethylsilane (TMS) (δ(H) 0.00 ppm) or $CHCl_3$ (δ(H) 7.26 ppm). ^{13}C NMR spectra were recorded on a 100 MHz, 125 MHz and 150 MHz spectrometer at 298 K in $CDCl_3$; chemical shifts (δ, ppm) were reported relative to $CHCl_3$ (δ(C) 77.23 ppm, central line of triplet. Multiplicities were given as: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplets), dd (doublet of doublets), dt (doublet of triplets), and br (broad). Coupling constants (*J*) were recorded in Hertz (Hz).

Enantiomeric excesses were determined by HPLC analysis using Dionex (Ultimate 3000) instrument with chiral columns in comparison with authentic racemic compounds. High resolution mass spectra (HRMS) were recorded in Q-TOF using electron spray ionization (ESI) technique. IR spectra were recorded on Perkin Elmer Instrument at normal temperature by making KBr pellet and grinding the sample with KBr (IR Grade). Melting points were measured with a Mel-Tem capillary melting point apparatus.

Single crystal X-ray data were collected using Bruker SMART APEXII CCD diffractometer, which is equipped with 1.75 kW sealed-tube Mo-Kα irradiation (λ = 0.71073 Å) at 298(2) K and the structure was solved by direct methods using SHELXS-2014 (Göttingen, Germany) and refined with full-matrix least-squares on F^2 using SHELXL-2014.

A. General procedure for the synthesis of *trans*-γ-hydroxyenones 1a-1m

Trans-γ-hydroxyenones were prepared according to the reported procedure.[16]

B. General procedure for the synthesis of *trans*-δ-hydroxyenones 4a-4e

Trans-δ-hydroxyenones were prepared according to literature procedure.[17]

C. General procedure for the synthesis of α-nitroketones 2a-2r

α-nitroketones were prepared according to reported procedure.[18]

D. General procedure for Michael/Acyl transfer products 3a-3z'''' and 5a-5o

To a stirred solution of compound **1** or **4** (0.1 mmol) and α-nitroketone **2** (0.12 mmol) in toluene (0.5 mL), catalyst **XIII** (10 mol%) was added at room temperature. The resulting reaction mixture was stirred at this temperature for 2-5 days and the progress of the reaction was monitored by TLC. Upon completion, the crude product was subjected to silica gel column chromatography using hexane/ethyl acetate to obtain the desired product.

E. General procedure for the synthesis of compounds 7

This compound was prepared according to a modified procedure.[14,19]

To a stirred solution of **3a** (0.1 mmol) in THF (7 mL) and saturated NH_4Cl (7 mL), activated Zn was added. The reaction mixture was stirred at rt for 1.5 h. The crude reaction mixture was filtered through celite and concentrated in rotavapour under reduced pressure. Then the residue was dissolved in EtOAc and washed with water. The organic layer was dried over Na_2SO_4 and concentrated. Without further purification, the next step was performed. The residue was dissolved in DCM (0.5 mL). After that TsCl (1.1 equiv.) and Et_3N (1.1 equiv.) were added to it at rt. The reaction mixture was stirred for overnight. Then, the residue was purified by flash column chromatography using 10% ethyl acetate/hexane to obtain the desired product **7**.

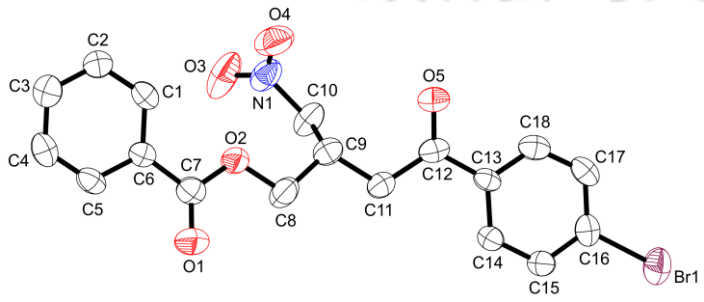
F. General procedure for the synthesis of compounds 8

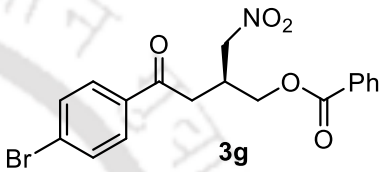
This compound was prepared according to literature procedure.[20]

To a stirred solution NaOH (40 mg) in 1.5 mL water, a solution of compound **3a** (0.2 mmol) in THF (1.5 mL) was added to it slowly. Then the reaction mixture was stirred at rt for 45 minutes. The reaction mixture was acidified to pH = 4 by adding 1.5 M H_2SO_4,

brine was added, and the mixture was extracted with ethyl acetate. The organic layer was dried with Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography using 25% ethyl acetate and hexane as eluent to obtain the desired product **8**.

Crystal structure of compound (*S*)-4-(4-bromophenyl)-2-(nitromethyl)-4-oxobutyl benzoate (3g)





ORTEP crystal structure

Table 1. Crystal data and structure refinement for compound 3g

Parameters	**3g**
Formula	$C_{18}H_{16}BrO_5N$
Fw	406.22
Crystal system	monoclinic
Space group	$P2_1$
a/Å	10.8540(5)
b/Å	5.5969(3)
c/Å	15.0011(9)
α/°	90.00
β/°	107.715(6)
γ/°	90.00
V/Å^3	868.09(8)
Z	2

D_c/g cm^{-3}	1.554
μ Mo K_α/mm^{-1}	2.396
F000	412.0
T/K	293(2)
θ max.	24.980
Total no. of reflections	3255
Independent reflections	2573
Parameters refined	226
R_1, I > 2σ(I)	0.0592
wR_2, I > 2σ(I)	0.0834
GOF (F^2)	1.034
CCDC No.	1578993

5.6 References

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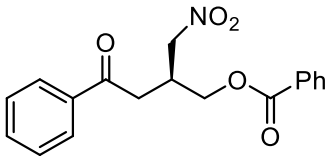
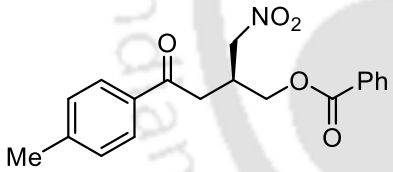
5.7 Characterization Data of Products

(S)-2-(nitromethyl)-4-oxo-4-phenylbutyl benzoate (3a)



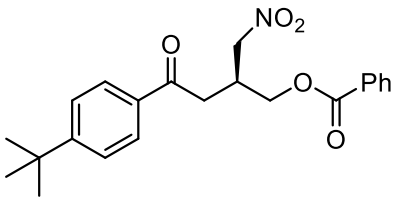
This compound was prepared according to the general procedure D. Reaction was completed after 2 d. Analytical TLC on silica gel using 12% ethyl acetate/hexane. White solid (30.5 mg, 93% yield); **Mp:** 71-73 °C; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.00 (d, *J* = 7.2 Hz, 2H), 7.96 (d, *J* = 7.3 Hz, 2H), 7.59 (q, *J* = 7.5 Hz, 2H), 7.47 (dt, *J* = 15.8, 7.8 Hz, 4H), 4.72 (d, *J* = 6.0 Hz, 2H), 4.53 – 4.47 (m, 2H), 3.42 (dt, *J* = 12.0, 6.0 Hz, 1H), 3.28 (d, *J* = 6.5 Hz, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 196.9, 166.3, 136.5, 133.9, 133.6, 129.9, 129.6, 129.0, 128.8, 128.3, 76.4, 64.8, 37.2, 33.4; **FT-IR (thin film):** 1719, 1678, 1539, 1451, 1385, 1283, 1178, 1111, 1070 1002, 760, 711, 688 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{18}H_{18}NO_5$ $[M+H]^+$ 328.1179; found: 328.1181; The ee value 96% (t_{minor} = 62.7 min, t_{major} = 68.3 min) was determined by HPLC analysis using Daicel Chiralpak ID with hexane/^{i}PrOH (90:10) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^{o}C.

(S)-2-(nitromethyl)-4-oxo-4-(p-tolyl)butyl benzoate (3b)



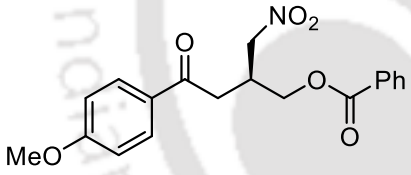
This compound was prepared according to the general procedure D. Reaction was completed after 3 d. Analytical TLC on silica gel using 12% ethyl acetate/hexane. White solid (26 mg, 76% yield); **Mp:** 80-82 °C; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.96 (d, *J* = 7.3 Hz, 2H), 7.88 (d, *J* = 8.2 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 2H), 7.25 (d, *J* = 8.1 Hz, 2H), 4.71 (d, *J* = 6.3 Hz, 2H), 4.51 – 4.45 (m, 2H), 3.41 (dt, *J* = 11.9, 6.1 Hz, 1H), 3.27 (d, *J* = 6.4 Hz, 2H), 2.42 (s, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 196.6, 166.3, 144.9, 134.0, 133.6, 129.8, 129.7, 129.6, 128.7, 128.4, 76.5, 64.9, 37.1, 33.5, 21.9; **FT-IR (thin film):** 1712, 1682, 1549, 1363, 1279, 1224, 1180, 1110, 1000, 755, 639 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{19}H_{20}NO_5$ $[M+H]^+$ 342.1336; found: 342.1346; The ee value 96% (t_{minor} = 66.9 min, t_{major} = 76.5 min) was determined by HPLC analysis using Daicel Chiralpak ID with hexane/^{i}PrOH (90:10) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^{o}C.

(S)-4-(4-(tert-butyl)phenyl)-2-(nitromethyl)-4-oxobutyl benzoate (3c)



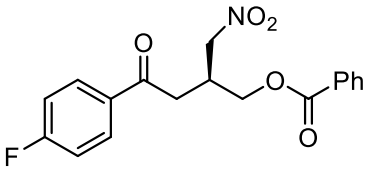
This compound was prepared according to the general procedure D. Reaction was completed after 3 d. Analytical TLC on silica gel using 12% ethyl acetate/hexane. White solid (24 mg, 63% yield); **Mp:** 80-82 °C; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.99 (d, *J* = 7.2 Hz, 2H), 7.90 (d, *J* = 8.5 Hz, 2H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.49 (d, *J* = 8.5 Hz, 2H), 7.45 (t, *J* = 7.8 Hz, 2H), 4.71 (d, *J* = 6.0 Hz, 2H), 4.53 – 4.46 (m, 2H), 3.41 (dt, *J* = 11.9, 6.1 Hz, 1H), 3.25 (d, *J* = 6.5 Hz, 2H), 1.34 (s, 9H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 196.6, 166.3, 157.9, 133.9, 133.6, 129.8, 129.6, 128.7, 128.3, 125.9, 76.5, 64.9, 37.1, 35.4, 33.5, 31.3; **FT-IR (thin film):** 1708, 1676, 1604, 1547, 1279, 1216, 1114, 1002, 825, 713, 581 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{22}H_{26}NO_5$ $[M+H]^+$ 384.1805; found: 384.1801; The ee value 96% (t_{minor} = 20.5 min, t_{major} = 25.3 min) was determined by HPLC analysis using Daicel Chiralpak ID with hexane/^{i}PrOH (80:20) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C.

(S)-4-(4-methoxyphenyl)-2-(nitromethyl)-4-oxobutyl benzoate (3d)



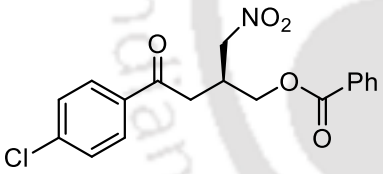
This compound was prepared according to the general procedure D. Reaction was completed after 5 d. Analytical TLC on silica gel using 18% ethyl acetate/hexane. White solid (19 mg, 53% yield); **Mp:** 87-89 °C; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.00 (d, *J* = 7.2 Hz, 2H), 7.94 (d, *J* = 8.9 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.8 Hz, 2H), 6.94 (d, *J* = 8.9 Hz, 2H), 4.71 (d, *J* = 6.0 Hz, 2H), 4.53 – 4.45 (m, 2H), 3.88 (s, 3H), 3.41 (dt, *J* = 12.0, 6.1 Hz, 1H), 3.22 (d, *J* = 6.5 Hz, 2H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 195.4, 166.3, 164.2, 133.6, 130.6, 129.8, 129.7, 129.6, 128.8, 114.1, 76.5, 64.9, 55.8, 36.8, 33.5; **FT-IR (thin film):** 1709, 1670, 1602, 1553, 1363, 1275, 1178, 1121, 1027, 996, 817, 711 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{19}H_{20}NO_6$ $[M+H]^+$ 358.1285; found: 358.1293; The ee value 96% (t_{minor} = 42.4 min, t_{major} = 47.5 min) was determined by HPLC analysis using Daicel Chiralpak ID with hexane/^{i}PrOH (70:30) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C.

(S)-4-(4-fluorophenyl)-2-(nitromethyl)-4-oxobutyl benzoate (3e)



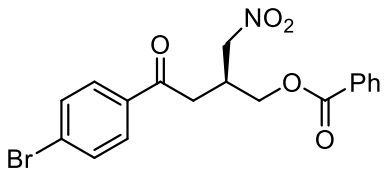
This compound was prepared according to the general procedure D. Reaction was completed after 3 d. Analytical TLC on silica gel using 10% ethyl acetate/hexane. White solid (25 mg, 72% yield); **Mp:** 75-77 °C; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.99 (dd, *J* = 8.5, 5.4 Hz, 4H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 7.15 (t, *J* = 8.6 Hz, 2H), 4.74 – 4.69 (m, 2H), 4.50 (d, *J* = 5.6 Hz, 2H), 3.41 (dt, *J* = 12.0, 6.0 Hz, 1H), 3.25 (d, *J* = 6.5 Hz, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 195.4, 167.3, 166.3 (d, *J* = 152.3 Hz), 133.7, 132.9 (d, *J* = 3.0 Hz), 131.0 (d, *J* = 10.5 Hz), 130.9, 129.8, 129.6, 128.8, 116.2 (d, *J* = 25.5 Hz), 76.4, 64.8, 37.1, 33.4; **FT-IR (thin film):** 1722, 1686, 1596, 1549, 1283, 1228, 1112, 1000, 841, 713 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{18}H_{17}NFO_5$ $[M+H]^+$ 346.1085; found: 346.1091; The ee value 94% (t_{minor} = 35.0 min, t_{major} = 39.1 min) was determined by HPLC analysis using Daicel Chiralpak ID with hexane/^{i}PrOH (85:15) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C.

(S)-4-(4-chlorophenyl)-2-(nitromethyl)-4-oxobutyl benzoate (3f)



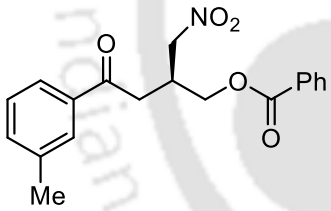
This compound was prepared according to the general procedure D. Reaction was completed after 3 d. Analytical TLC on silica gel using 10% ethyl acetate/hexane. White solid (27 mg, 75% yield); **Mp:** 95-97 °C; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.99 (d, *J* = 7.2 Hz, 2H), 7.90 (d, *J* = 8.6 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.4 Hz, 4H), 4.75 – 4.68 (m, 2H), 4.50 (d, *J* = 5.6 Hz, 2H), 3.40 (dt, *J* = 12.0, 6.0 Hz, 1H), 3.24 (d, *J* = 6.5 Hz, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 195.9, 166.3, 140.5, 134.8, 133.7, 129.8, 129.7, 129.6, 129.4, 128.8, 76.4, 64.7, 37.2, 33.4; **FT-IR (thin film):** 1714, 1682, 1555, 1317, 1279, 1220, 1114, 996, 817, 711 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{18}H_{17}NClO_5$ $[M+H]^+$ 362.0790; found: 362.0786; The ee value 94% (t_{minor} = 36.7 min, t_{major} = 42.8 min) was determined by HPLC analysis using Daicel Chiralpak ID with hexane/^{i}PrOH (85:15) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C.

(S)-4-(4-bromophenyl)-2-(nitromethyl)-4-oxobutyl benzoate (3g)



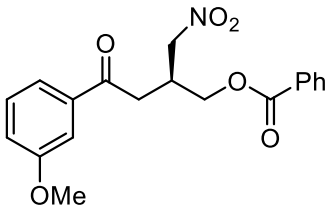
This compound was prepared according to the general procedure D. Reaction was completed after 3 d. Analytical TLC on silica gel using 10% ethyl acetate/hexane. White solid (34 mg, 84% yield); **Mp:** 105-107 °C; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.99 (d, *J* = 7.2 Hz, 2H), 7.82 (d, *J* = 8.6 Hz, 2H), 7.62 (d, *J* = 8.6 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 4.74 – 4.67 (m, 2H), 4.50 (d, *J* = 5.6 Hz, 2H), 3.40 (dt, *J* = 12.0, 6.0 Hz, 1H), 3.24 (d, *J* = 6.5 Hz, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 195.9, 166.3, 135.2, 133.7, 132.4, 129.8, 129.7, 129.6, 129.2, 128.8, 76.4, 64.7, 37.2, 33.4; ; **FT-IR (thin film):** 1713, 1684, 1556, 1383, 1278, 1114, 995, 815, 713 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{18}H_{17}NBrO_5$ $[M+H]^+$ 406.0285; found: 406.0279; The ee value 94% (t_{minor} = 62.6 min, t_{major} = 73.7 min) was determined by HPLC analysis using Daicel Chiralpak ID with hexane/^{i}PrOH (90:10) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^{o}C.

(S)-2-(nitromethyl)-4-oxo-4-(m-tolyl)butyl benzoate (3h)



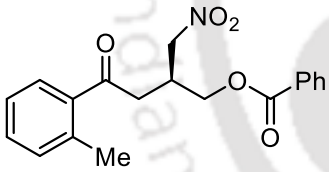
This compound was prepared according to the general procedure D. Reaction was completed after 3 d. Analytical TLC on silica gel using 12% ethyl acetate/hexane. Colorless oil (26 mg, 76% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.00 (d, *J* = 7.2 Hz, 2H), 7.75 (d, *J* = 9.0 Hz, 2H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 7.41 (d, *J* = 7.5 Hz, 1H), 7.36 (t, *J* = 7.5 Hz, 1H), 4.72 (d, *J* = 6.0 Hz, 2H), 4.53 – 4.46 (m, 2H), 3.41 (dt, *J* = 12.0, 6.0 Hz, 1H), 3.26 (d, *J* = 6.9 Hz, 2H), 2.41 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 197.2, 166.3, 138.9, 136.5, 134.7, 133.6, 129.8, 129.6, 128.9, 128.8, 128.7, 125.5, 76.4, 64.8, 37.2, 33.4, 21.6; **FT-IR (thin film):** 1723, 1685, 1549, 1380, 1272, 1165, 1115, 1033, 715, cm^{-1}; **HRMS (+ESI):** Calcd for $C_{19}H_{20}NO_5$ $[M+H]^+$ 342.1336; found: 342.1335; The ee value 92% (t_{minor} = 28.8 min, t_{major} = 31.9 min) was determined by HPLC analysis using Daicel Chiralpak ID with hexane/^{i}PrOH (80:20) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^{o}C.

(S)-4-(3-methoxyphenyl)-2-(nitromethyl)-4-oxobutyl benzoate (3i)



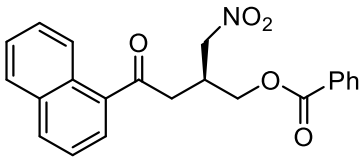
This compound was prepared according to the general procedure D. Reaction was completed after 3 d. Analytical TLC on silica gel using 18% ethyl acetate/hexane. White solid (22 mg, 61% yield); **Mp:** 64-66 °C; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.00 (d, *J* = 7.4 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.53 (d, *J* = 7.6 Hz, 1H), 7.46 (dd, *J* = 14.1, 6.3 Hz, 3H), 7.38 (t, *J* = 7.9 Hz, 1H), 7.14 (dd, *J* = 8.2, 2.4 Hz, 1H), 4.71 (dd, *J* = 6.0, 1.2 Hz, 2H), 4.53 – 4.45 (m, 2H), 3.85 (s, 3H), 3.42 (dt, *J* = 11.9, 6.1 Hz, 1H), 3.26 (d, *J* = 6.5 Hz, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 196.8, 166.3, 160.2, 137.9, 133.6, 130.0, 129.9, 129.7, 128.7, 120.8, 120.4, 112.6, 76.4, 64.8, 55.7, 37.4, 33.6; **FT-IR (thin film):** 1716, 1680, 1600, 1539, 1373, 1279, 1116, 1032, 709 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{19}H_{20}NO_6$ $[M+H]^+$ 358.1285; found: 358.1289; The ee value 96% (t_{minor} = 28.8 min, t_{major} = 33.8 min) was determined by HPLC analysis using Daicel Chiralpak ID with hexane/^{i}PrOH (70:30) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C.

(S)-2-(nitromethyl)-4-oxo-4-(o-tolyl)butyl benzoate (3j)



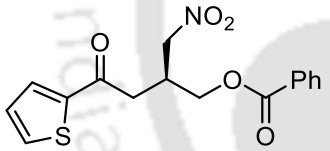
This compound was prepared according to the general procedure D. Reaction was completed after 3 d. Analytical TLC on silica gel using 10% ethyl acetate/hexane. Brownish oil (22 mg, 64% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.00 (d, *J* = 7.2 Hz, 2H), 7.66 (d, *J* = 7.7 Hz, 1H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 7.41 (t, *J* = 7.5 Hz, 1H), 7.30 – 7.26 (m, 2H), 4.71 (qd, *J* = 12.8, 6.0 Hz, 2H), 4.49 (d, *J* = 6.2 Hz, 2H), 3.39 (dt, *J* = 11.9, 6.0 Hz, 1H), 3.20 (d, *J* = 6.6 Hz, 2H), 2.52 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 200.5, 166.3, 138.9, 136.9, 133.6, 132.5, 132.2, 129.8, 129.6, 128.8, 128.7, 126.1, 76.4, 64.8, 39.8, 33.6, 21.7; **FT-IR (thin film):** 1721, 1685, 1552, 1452, 1381, 1272, 1112, 756, 713 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{19}H_{20}NO_5$ $[M+H]^+$ 342.1336; found: 342.1339; The ee value 92% (t_{minor} = 18.3 min, t_{major} = 20.7 min) was determined by HPLC analysis using Daicel Chiralpak ID with hexane/^{i}PrOH (80:20) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C.

(S)-4-(naphthalen-1-yl)-2-(nitromethyl)-4-oxobutyl benzoate (3k)



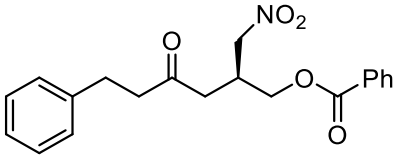
This compound was prepared according to the general procedure D. Reaction was completed after 5 d. Analytical TLC on silica gel using 15% ethyl acetate/hexane. Brownish sticky oil (22 mg, 58% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.64 (d, *J* = 8.8 Hz, 1H), 8.04 – 7.99 (m, 3H), 7.92 – 7.87 (m, 2H), 7.63 – 7.54 (m, 3H), 7.50 (dd, *J* = 8.1, 7.3 Hz, 1H), 7.45 (t, *J* = 7.8 Hz, 2H), 4.81 – 4.73 (m, 2H), 4.55 (d, *J* = 5.7 Hz, 2H), 3.49 (dq, *J* = 11.9, 6.1 Hz, 1H), 3.37 (d, *J* = 6.6 Hz, 2H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 200.8, 166.3, 134.9, 134.2, 133.7, 133.6, 130.3, 129.8, 129.6, 128.8, 128.7, 128.6, 128.3, 126.9, 125.8, 124.5, 76.5, 64.8, 40.4, 33.8; **FT-IR (thin film):** 1721, 1681, 1552, 1381, 1272, 1176, 1111, 728, 713 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{22}H_{20}NO_5$ $[M+H]^+$ 378.1336; found: 378.1341; The ee value 91% (t_{minor} = 30.4 min, t_{major} = 51.6 min) was determined by HPLC analysis using Daicel Chiralpak ID with hexane/^{i}PrOH (80:20) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^{o}C.

(S)-2-(nitromethyl)-4-oxo-4-(thiophen-2-yl)butyl benzoate (3l)



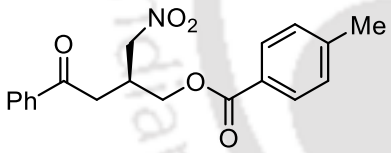
This compound was prepared according to the general procedure D. Reaction was completed after 4 d. Analytical TLC on silica gel using 15% ethyl acetate/hexane. White solid (23 mg, 72% yield); **Mp:** 52-54 °C; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.99 (d, *J* = 7.2 Hz, 2H), 7.74 (d, *J* = 3.8 Hz, 1H), 7.69 (d, *J* = 4.9 Hz, 1H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.8 Hz, 2H), 7.14 (dd, *J* = 4.8, 4.0 Hz, 1H), 4.71 (d, *J* = 6.0 Hz, 2H), 4.52 – 4.45 (m, 2H), 3.39 (dp, *J* = 12.1, 6.1 Hz, 1H), 3.22 (d, *J* = 6.5 Hz, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 189.8, 166.3, 143.6, 134.7, 133.6, 132.6, 129.8, 129.6, 128.8, 128.6, 76.3, 64.7, 37.9, 33.7; **FT-IR (thin film):** 1721, 1662, 1552, 1416, 1272, 1113, 1070, 856, 713 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{16}H_{16}NSO_5$ $[M+H]^+$ 334.0744; found: 334.0747; The ee value 92% (t_{minor} = 47.0 min, t_{major} = 56.4 min) was determined by HPLC analysis using Daicel Chiralpak ID with hexane/^{i}PrOH (80:20) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^{o}C.

(S)-2-(nitromethyl)-4-oxo-6-phenylhexyl benzoate (3m)



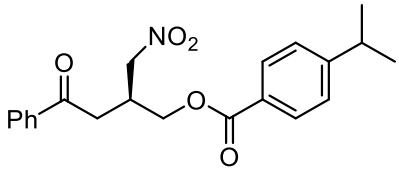
This compound was prepared according to the general procedure D. Reaction was completed after 4 d. Analytical TLC on silica gel using 15% ethyl acetate/hexane. Colorless oil (18 mg, 51% yield); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.96 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.15 (dd, *J* = 18.5, 7.2 Hz, 3H), 4.54 (qd, *J* = 12.7, 6.1 Hz, 2H), 4.33 (d, *J* = 5.6 Hz, 2H), 3.16 (dt, *J* = 12.1, 6.1 Hz, 1H), 2.89 (t, *J* = 7.5 Hz, 2H), 2.75 (t, *J* = 7.5 Hz, 2H), 2.62 (d, *J* = 7.0 Hz, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 207.0, 166.2, 140.6, 133.7, 129.8, 129.5, 128.8, 128.7, 128.5, 126.5, 76.2, 64.5, 44.8, 41.4, 32.9, 29.9; **FT-IR (thin film):** 1718, 1602, 1552, 1452, 1380, 1272, 1112, 1026, 713 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{20}H_{25}N_2O_5$ $[M+NH_4]^+$ 373.1758; found: 373.1755; The ee value 62% (t_{minor} = 12.5 min, t_{major} = 14.0 min) was determined by HPLC analysis using Daicel Chiralpak ID with hexane/^{i}PrOH (85:15) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^{o}C.

(S)-2-(nitromethyl)-4-oxo-4-phenylbutyl 4-methylbenzoate (3n)



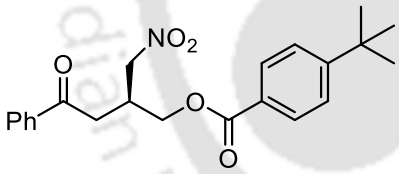
This compound was prepared according to the general procedure D. Reaction was completed after 2 d. Analytical TLC on silica gel using 12% ethyl acetate/hexane. White solid (29 mg, 85% yield); **Mp:** 77-79 °C; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.96 (d, *J* = 7.3 Hz, 2H), 7.88 (d, *J* = 8.1 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 4.71 (d, *J* = 6.3 Hz, 2H), 4.51 – 4.45 (m, 2H), 3.41 (dt, *J* = 12.0, 6.0 Hz, 1H), 3.27 (d, *J* = 6.5 Hz, 2H), 2.42 (s, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 197.0, 166.4, 144.4, 136.5, 133.9, 129.9, 129.5, 129.0, 128.3, 126.9, 76.4, 64.6, 37.2, 33.4, 21.9; **FT-IR (thin film):** 1720, 1681, 1610, 1556, 1383, 1275, 1211, 1180, 1111, 1002, 753, 688 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{19}H_{20}NO_5$ $[M+H]^+$ 342.1336; found: 342.1338; The ee value 96% (t_{minor} = 64.1 min, t_{major} = 77.5 min) was determined by HPLC analysis using Daicel Chiralpak ID with hexane/^{i}PrOH (90:10) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^{o}C.

(S)-2-(nitromethyl)-4-oxo-4-phenylbutyl 4-isopropylbenzoate (3o)



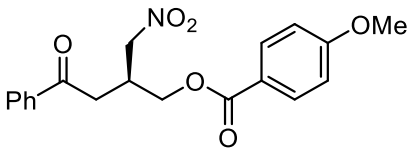
This compound was prepared according to the general procedure D. Reaction was completed after 2 d. Analytical TLC on silica gel using 12% ethyl acetate/hexane. White solid (33.5 mg, 90% yield); **Mp:** 82-84 °C; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.96 (d, *J* = 7.3 Hz, 2H), 7.92 (d, *J* = 8.3 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 2H), 7.30 (d, *J* = 8.2 Hz, 2H), 4.71 (d, *J* = 6.2 Hz, 2H), 4.51 – 4.46 (m, 2H), 3.41 (dt, *J* = 12.1, 6.1 Hz, 1H), 3.27 (d, *J* = 6.4 Hz, 2H), 2.97 (dt, *J* = 13.8, 6.9 Hz, 1H), 1.27 (d, *J* = 6.9 Hz, 6H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 197.0, 166.3, 155.2, 136.5, 133.9, 130.0, 129.0, 128.3, 127.2, 126.9, 76.4, 64.6, 37.2, 34.5, 33.5, 23.9; **FT-IR (thin film):** 1710, 1678, 1608, 1551, 1449, 1417, 1371, 1269, 1228, 1186, 1118, 1006, 851, 749, 685 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{21}H_{24}NO_5$ $[M+H]^+$ 370.1649; found: 370.1653; The ee value 94% (t_{minor} = 24.2 min, t_{major} = 34.3 min) was determined by HPLC analysis using Daicel Chiralpak ID with hexane/^{i}PrOH (80:20) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^{o}C.

(S)-2-(nitromethyl)-4-oxo-4-phenylbutyl 4-(tert-butyl)benzoate (3p)



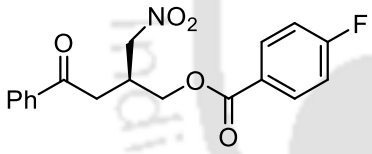
This compound was prepared according to the general procedure D. Reaction was completed after 2 d. Analytical TLC on silica gel using 12% ethyl acetate/hexane. White solid (32 mg, 83% yield); **Mp:** 97-99 °C; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.94 (dd, *J* = 19.3, 7.9 Hz, 4H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.48 (dd, *J* = 12.6, 8.2 Hz, 4H), 4.71 (d, *J* = 6.0 Hz, 2H), 4.51 – 4.46 (m, 2H), 3.41 (dd, *J* = 12.0, 6.0 Hz, 1H), 3.27 (d, *J* = 6.5 Hz, 2H), 1.34 (s, 9H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 197.0, 166.3, 157.4, 136.5, 133.9, 129.7, 128.9, 128.3, 126.8, 125.7, 76.5, 64.6, 37.2, 35.3, 33.5, 31.3; **FT-IR (thin film):** 1707, 1679, 1610, 1544, 1284, 1211, 1120, 1002, 852, 746, 688 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{22}H_{26}NO_5$ $[M+H]^+$ 384.1805; found: 384.1812; The ee value 94% (t_{minor} = 18.7 min, t_{major} = 26.0 min) was determined by HPLC analysis using Daicel Chiralpak ID with hexane/^{i}PrOH (80:20) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^{o}C.

(S)-2-(nitromethyl)-4-oxo-4-phenylbutyl 4-methoxybenzoate (3q)



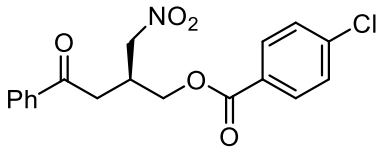
This compound was prepared according to the general procedure D. Reaction was completed after 2 d. Analytical TLC on silica gel using 18% ethyl acetate/hexane. White solid (32.5 mg, 91% yield); **Mp:** 116-118 °C; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.96 (dd, *J* = 8.0, 6.4 Hz, 4H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 2H), 6.93 (d, *J* = 8.9 Hz, 2H), 4.71 (d, *J* = 6.3 Hz, 2H), 4.50 – 4.44 (m, 2H), 3.87 (s, 3H), 3.41 (dt, *J* = 12.0, 6.1 Hz, 1H), 3.27 (d, *J* = 6.5 Hz, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 197.0, 166.0, 163.9, 136.5, 133.9, 131.9, 129.0, 128.3, 121.9, 114.0, 76.5, 64.6, 55.7, 37.2, 33.5; **FT-IR (thin film):** 1750, 1600, 1553, 1510, 1379, 1320, 1256, 1165, 1109, 1008, 848, 768, 690, 611 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{19}H_{20}NO_6$ $[M+H]^+$ 358.1285; found: 358.1286; The ee value 96% (t_{minor} = 57.3 min, t_{major} = 75.6 min) was determined by HPLC analysis using Daicel Chiralpak ID with hexane/^{i}PrOH (80:20) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C.

(S)-2-(nitromethyl)-4-oxo-4-phenylbutyl 4-fluorobenzoate (3r)



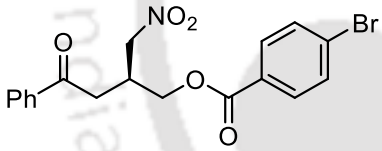
This compound was prepared according to the general procedure D. Reaction was completed after 3 d. Analytical TLC on silica gel using 12% ethyl acetate/hexane. Semi solid (28.5 mg, 82% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.00 (dd, *J* = 8.7, 5.4 Hz, 2H), 7.96 (d, *J* = 7.7 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 2H), 7.12 (t, *J* = 8.6 Hz, 2H), 4.71 (d, *J* = 6.0 Hz, 2H), 4.52 – 4.46 (m, 2H), 3.41 (dq, *J* = 12.1, 6.1 Hz, 1H), 3.27 (dd, *J* = 6.5, 1.2 Hz, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 196.9, 167.3, 165.3 (d, *J* = 18.0 Hz), 136.5, 134.0, 132.5 (d, *J* = 10.5 Hz), 129.1, 128.3, 125.9, 116.0 (d, *J* = 27.0 Hz), 76.5, 65.1, 37.2, 33.5; **FT-IR (thin film):** 1719, 1686, 1602, 1549, 1509, 1377, 1276, 1231, 1121, 1002, 853, 763, 688, 608 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{18}H_{17}NFO_5$ $[M+H]^+$ 346.1085; found: 346.1080; The ee value 90% (t_{minor} = 23.7 min, t_{major} = 27.6 min) was determined by HPLC analysis using Daicel Chiralpak ID with hexane/^{i}PrOH (80:20) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C.

(S)-2-(nitromethyl)-4-oxo-4-phenylbutyl 4-chlorobenzoate (3s)



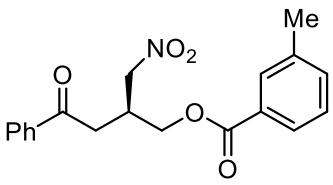
This compound was prepared according to the general procedure D. Reaction was completed after 3 d. Analytical TLC on silica gel using 12% ethyl acetate/hexane. White solid (29.5 mg, 81% yield); **Mp:** 81-83 °C; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.96 (d, *J* = 7.4 Hz, 2H), 7.92 (d, *J* = 8.6 Hz, 2H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.8 Hz, 2H), 7.43 (d, *J* = 8.6 Hz, 2H), 4.71 (d, *J* = 6.0 Hz, 2H), 4.53 – 4.46 (m, 2H), 3.42 (dt, *J* = 11.9, 6.0 Hz, 1H), 3.27 (dd, *J* = 6.4, 2.1 Hz, 2H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 196.9, 165.5, 140.1, 136.5, 134.0, 131.2, 129.1, 129.0, 128.3, 128.1, 76.5, 65.2, 37.2, 33.4; **FT-IR (thin film):** 1714, 1682, 1592, 1551, 1377, 1273, 1108, 998, 761, 687 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{18}H_{17}NClO_5$ $[M+H]^+$ 362.0790; found: 362.0788; The ee value 95% (t_{minor} = 25.7 min, t_{major} = 32.2 min) was determined by HPLC analysis using Daicel Chiralpak ID with hexane/^{i}PrOH (80:20) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^{o}C.

(S)-2-(nitromethyl)-4-oxo-4-phenylbutyl 4-bromobenzoate (3t)



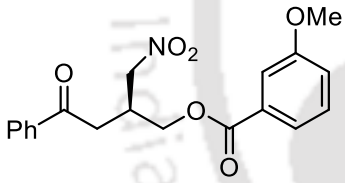
This compound was prepared according to the general procedure D. Reaction was completed after 3 d. Analytical TLC on silica gel using 12% ethyl acetate/hexane. Yellow crystalline solid (31.5 mg, 78% yield); **Mp:** 101-103 °C; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.95 (d, *J* = 7.4 Hz, 2H), 7.84 (d, *J* = 8.5 Hz, 2H), 7.60 (dd, *J* = 12.4, 8.0 Hz, 3H), 7.49 (t, *J* = 7.8 Hz, 2H), 4.71 (d, *J* = 6.0 Hz, 2H), 4.53 – 4.45 (m, 2H), 3.42 (dt, *J* = 11.8, 6.0 Hz, 1H), 3.27 (dd, *J* = 6.4, 2.3 Hz, 2H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 196.9, 165.6, 136.5, 134.0, 132.1, 131.3, 129.1, 128.8, 128.5, 128.3, 76.5, 65.2, 37.2, 33.4; **FT-IR (thin film):** 1716, 1683, 1589, 1552, 1378, 1277, 1228, 1104, 1010, 847, 758, 692 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{18}H_{17}NBrO_5$ $[M+H]^+$ 406.0285; found: 406.0282; The ee value 96% (t_{minor} = 28.8 min, t_{major} = 37.3 min) was determined by HPLC analysis using Daicel Chiralpak ID with hexane/^{i}PrOH (80:20) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^{o}C.

(S)-2-(nitromethyl)-4-oxo-4-phenylbutyl 3-methylbenzoate (3u)



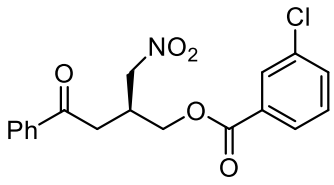
This compound was prepared according to the general procedure D. Reaction was completed after 2 d. Analytical TLC on silica gel using 12% ethyl acetate/hexane. White solid (28 mg, 82% yield); **Mp:** 53-55 °C; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.96 (d, *J* = 7.4 Hz, 1H), 7.79 (d, *J* = 10.4 Hz, 1H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 1H), 7.39 (d, *J* = 7.6 Hz, 1H), 7.34 (t, *J* = 7.6 Hz, 1H), 4.72 (d, *J* = 6.0 Hz, 1H), 4.49 (d, *J* = 5.6 Hz, 1H), 3.42 (dt, *J* = 12.0, 6.1 Hz, 1H), 3.28 (d, *J* = 6.0 Hz, 1H), 2.40 (s, 1H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 196.9, 166.5, 138.6, 136.5, 134.4, 133.9, 130.4, 129.5, 129.0, 128.6, 128.3, 126.9, 76.4, 64.7, 37.2, 33.4, 21.5; **FT-IR (thin film):** 1716, 1680, 1555, 1383, 1281, 1206, 1110, 998, 741, 687 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{19}H_{20}NO_5$ $[M+H]^+$ 342.1336; found: 342.1342; The ee value 92% (t_{minor} = 16.7 min, t_{major} = 17.9 min) was determined by HPLC analysis using Daicel Chiralpak IA with hexane/^{i}PrOH (90:10) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^{o}C.

(S)-2-(nitromethyl)-4-oxo-4-phenylbutyl 3-methoxybenzoate (3v)



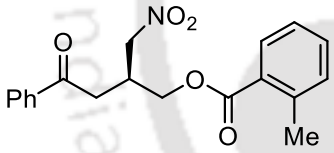
This compound was prepared according to the general procedure D. Reaction was completed after 2 d. Analytical TLC on silica gel using 18% ethyl acetate/hexane. White solid (31 mg, 86% yield); **Mp:** 63-65 °C; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.96 (d, *J* = 7.3 Hz, 2H), 7.60 (dd, *J* = 14.7, 7.4 Hz, 2H), 7.49 (dd, *J* = 14.3, 6.5 Hz, 3H), 7.36 (t, *J* = 8.0 Hz, 1H), 7.12 (dd, *J* = 8.2, 2.1 Hz, 1H), 4.71 (d, *J* = 6.0 Hz, 2H), 4.53 – 4.46 (m, 2H), 3.85 (s, 3H), 3.42 (dt, *J* = 11.9, 6.1 Hz, 1H), 3.28 (d, *J* = 6.5 Hz, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 196.9, 166.2, 159.9, 136.4, 133.9, 130.9, 129.7, 129.0, 128.3, 122.2, 120.1, 114.3, 76.5, 65.0, 55.7, 37.2, 33.4; **FT-IR (thin film):** 1711, 1680, 1596, 1541, 1490, 1371, 1279, 1229, 1072, 1004, 754, 688, cm^{-1}; **HRMS (+ESI):** Calcd for $C_{19}H_{20}NO_6$ $[M+H]^+$ 358.1285; found: 358.1292; The ee value 98% (t_{minor} = 44.9 min, t_{major} = 47.5 min) was determined by HPLC analysis using Daicel Chiralpak IA with hexane/^{i}PrOH (95:5) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^{o}C.

(S)-2-(nitromethyl)-4-oxo-4-phenylbutyl 3-chlorobenzoate (3w)



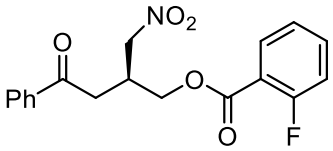
This compound was prepared according to the general procedure D. Reaction was completed after 3 d. Analytical TLC on silica gel using 12% ethyl acetate/hexane. Pale yellow sticky oil (24 mg, 66% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.96 (d, *J* = 6.9 Hz, 3H), 7.87 (d, *J* = 7.8 Hz, 1H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.56 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.49 (t, *J* = 7.8 Hz, 2H), 7.40 (t, *J* = 7.9 Hz, 1H), 4.72 (d, *J* = 6.0 Hz, 2H), 4.53 – 4.48 (m, 2H), 3.42 (dq, *J* = 12.0, 6.1 Hz, 1H), 3.28 (d, *J* = 6.5 Hz, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 196.9, 165.1, 136.4, 134.9, 133.9, 133.6, 131.4, 130.1, 129.9, 129.0, 128.3, 127.9, 76.4, 65.3, 37.2, 33.4; **FT-IR (thin film):** 1724, 1685, 1553, 1427, 1378, 1256, 1129, 1000, 749, 690 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{18}H_{17}NClO_5$ $[M+H]^+$ 362.0790; found: 362.0793; The ee value 96% (t_{minor} = 27.8 min, t_{major} = 29.7 min) was determined by HPLC analysis using Daicel Chiralpak ID with hexane/^{i}PrOH (80:20) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^{o}C.

(S)-2-(nitromethyl)-4-oxo-4-phenylbutyl 2-methylbenzoate (3x)



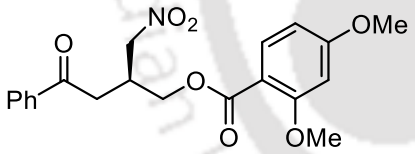
This compound was prepared according to the general procedure D. Reaction was completed after 2 d. Analytical TLC on silica gel using 12% ethyl acetate/hexane. Sticky oil (28.5 mg, 83% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.96 (d, *J* = 7.4 Hz, 2H), 7.86 (d, *J* = 8.3 Hz, 1H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 2H), 7.43 (t, *J* = 7.5 Hz, 1H), 7.28 – 7.25 (m, 2H), 4.71 (d, *J* = 6.0 Hz, 2H), 4.50 – 4.44 (m, 2H), 3.40 (dt, *J* = 12.0, 6.0 Hz, 1H), 3.27 (d, *J* = 7.1 Hz, 2H), 2.59 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 196.9, 167.0, 140.8, 136.5, 133.9, 132.7, 132.1, 130.7, 129.0, 128.9, 128.3, 126.1, 76.4, 64.5, 37.3, 33.4, 22.0; **FT-IR (thin film):** 1720, 1686, 1553, 1451, 1381, 1253, 1078, 741, 691 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{19}H_{20}NO_5$ $[M+H]^+$ 342.1336; found: 342.1338; The ee value 97% (t_{minor} = 39.7 min, t_{major} = 47.0 min) was determined by HPLC analysis using Daicel Chiralpak ID with hexane/^{i}PrOH (90:10) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^{o}C.

(S)-2-(nitromethyl)-4-oxo-4-phenylbutyl 2-fluorobenzoate (3y)



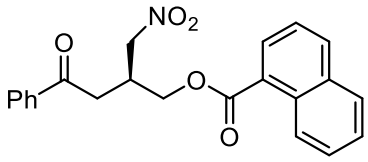
This compound was prepared according to the general procedure D. Reaction was completed after 3 d. Analytical TLC on silica gel using 12% ethyl acetate/hexane. Pale yellow sticky oil (28 mg, 81% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.97 (d, *J* = 7.3 Hz, 2H), 7.93 (td, *J* = 7.6, 1.7 Hz, 1H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.55 (ddd, *J* = 7.3, 4.9, 1.8 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 2H), 7.23 (t, *J* = 7.2 Hz, 1H), 7.15 (dd, *J* = 10.6, 8.7 Hz, 1H), 4.72 (d, *J* = 6.2 Hz, 2H), 4.54 – 4.48 (m, 2H), 3.41 (dt, *J* = 11.6, 5.9 Hz, 1H), 3.32 (dd, *J* = 18.1, 6.1 Hz, 1H), 3.26 (dd, *J* = 18.1, 6.9 Hz, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 197.0, 164.3 (d, *J* = 3.7 Hz), 161.1, 136.6, 135.1 (d, *J* = 8.7 Hz), 133.9, 132.5, 128.9, 128.3, 124.4 (d, *J* = 3.7 Hz), 118.3 (d, *J* = 10.0 Hz), 117.4, 117.3 (d, *J* = 22.5 Hz), 76.2, 65.0, 37.2, 33.2; **FT-IR (thin film):** 1724, 1685, 1612, 1552, 1454, 1379, 1279, 1128, 1083, 757, 690 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{18}H_{17}NFO_5$ $[M+H]^+$ 346.1085; found: 346.1086; The ee value 94% (t_{minor} = 29.7 min, t_{major} = 32.7 min) was determined by HPLC analysis using Daicel Chiralpak ID with hexane/^{i}PrOH (80:20) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^{o}C.

(S)-2-(nitromethyl)-4-oxo-4-phenylbutyl 2,4-dimethoxybenzoate (3z)



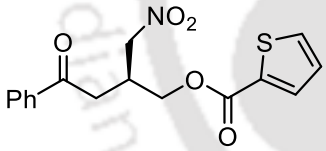
This compound was prepared according to the general procedure D. Reaction was completed after 3 d. Analytical TLC on silica gel using 20% ethyl acetate/hexane. Pale yellow sticky oil (30 mg, 78% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.96 (d, *J* = 7.3 Hz, 2H), 7.82 (d, *J* = 8.7 Hz, 1H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 2H), 6.51 (dd, *J* = 8.7, 2.3 Hz, 1H), 6.47 (d, *J* = 2.2 Hz, 1H), 4.72 (qd, *J* = 13.0, 6.1 Hz, 2H), 4.43 (dd, *J* = 5.4, 1.1 Hz, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 3.37 (dt, *J* = 11.9, 5.9 Hz, 1H), 3.30 (dd, *J* = 18.0, 6.0 Hz, 1H), 3.24 (dd, *J* = 18.0, 7.1 Hz, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 197.2, 165.6, 164.9, 161.6, 136.6, 134.2, 133.8, 128.9, 128.2, 111.9, 105.0, 99.2, 76.3, 64.2, 56.1, 55.7, 37.3, 33.4; **FT-IR (thin film):** 1721, 1687, 1609, 1552, 1381, 1272, 1212, 1139, 1081, 1028, 835, 756, 691, cm^{-1}; **HRMS (+ESI):** Calcd for $C_{20}H_{22}NO_7$ $[M+H]^+$ 388.1391; found: 388.1394; The ee value 93% (t_{minor} = 49.8 min, t_{major} = 61.3 min) was determined by HPLC analysis using Daicel Chiralpak ID with hexane/^{i}PrOH (65:35) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^{o}C.

(S)-2-(nitromethyl)-4-oxo-4-phenylbutyl 1-naphthoate (3z')



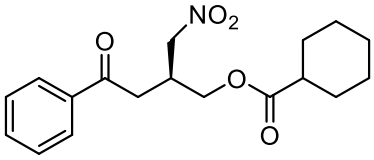
This compound was prepared according to the general procedure D. Reaction was completed after 3 d. Analytical TLC on silica gel using 15% ethyl acetate/hexane. White solid (28 mg, 74% yield); **Mp:** 90-92 °C; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.87 (d, *J* = 8.6 Hz, 1H), 8.13 (d, *J* = 7.2 Hz, 1H), 8.05 (d, *J* = 8.1 Hz, 1H), 7.97 (d, *J* = 7.3 Hz, 2H), 7.90 (d, *J* = 8.1 Hz, 1H), 7.60 (dd, *J* = 16.6, 7.4 Hz, 2H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.49 (dt, *J* = 19.2, 7.7 Hz, 3H), 4.75 (d, *J* = 6.0 Hz, 2H), 4.62 – 4.56 (m, 2H), 3.47 (dt, *J* = 12.0, 6.0 Hz, 1H), 3.35 – 3.27 (m, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 197.0, 167.0, 136.4, 134.1, 134.0, 133.9, 131.6, 130.4, 129.0, 128.8, 128.3, 128.2, 126.6, 126.4, 125.8, 124.7, 76.4, 64.7, 37.3, 33.4; **FT-IR (thin film):** 1715, 1682, 1547, 1379, 1240, 1203, 1137, 1002, 785, 754, 686 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{22}H_{20}NO_5$ $[M+H]^+$ 378.1336; found: 378.1333; The ee value 98% (t_{minor} = 38.7 min, t_{major} = 47.7 min) was determined by HPLC analysis using Daicel Chiralpak ID with hexane/^{i}PrOH (80:20) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C.

(S)-2-(nitromethyl)-4-oxo-4-phenylbutyl thiophene-2-carboxylate (3z'')



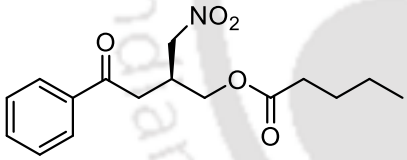
This compound was prepared according to the general procedure D. Reaction was completed after 2 d. Analytical TLC on silica gel using 15% ethyl acetate/hexane. White solid (29 mg, 87% yield); **Mp:** 57-59 °C; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.96 (d, *J* = 7.4 Hz, 2H), 7.80 (d, *J* = 3.7 Hz, 1H), 7.60 (dd, *J* = 10.2, 6.1 Hz, 2H), 7.49 (t, *J* = 7.8 Hz, 2H), 7.12 (dd, *J* = 4.8, 3.9 Hz, 1H), 4.70 (d, *J* = 6.2 Hz, 2H), 4.50 – 4.46 (m, 2H), 3.39 (dt, *J* = 12.0, 6.0 Hz, 1H), 3.26 (dd, *J* = 6.5, 3.2 Hz, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 196.9, 161.8, 136.4, 134.2, 133.9, 133.2, 132.9, 129.0, 128.3, 128.2, 76.3, 64.9, 37.1, 33.4: **FT-IR (thin film):** 1706, 1680, 1549, 1415, 1275, 1224, 1098, 998, 751, 729, 687 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{16}H_{16}NO_5S$ $[M+H]^+$ 334.0744; found: 334.0740; The ee value 96% (t_{minor} = 77.7 min, t_{major} = 84.8 min) was determined by HPLC analysis using Daicel Chiralpak ID with hexane/^{i}PrOH (90:10) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C.

(S)-2-(nitromethyl)-4-oxo-4-phenylbutyl cyclohexanecarboxylate (3z''')



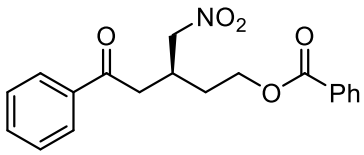
This compound was prepared according to the general procedure D. Reaction was completed after 4 d. Analytical TLC on silica gel using 12% ethyl acetate/hexane. White solid (21.5 mg, 65% yield); **Mp:** 50-52 °C; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.95 (d, *J* = 7.3 Hz, 2H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.8 Hz, 2H), 4.62 (d, *J* = 6.0 Hz, 2H), 4.22 (qd, *J* = 11.5, 5.6 Hz, 2H), 3.29 – 3.23 (m, 1H), 3.18 (d, *J* = 6.7 Hz, 2H), 2.30 (tt, *J* = 11.4, 3.6 Hz, 1H), 1.88 (d, *J* = 13.1 Hz, 2H), 1.78 – 1.72 (m, 2H), 1.64 (d, *J* = 11.8 Hz, 1H), 1.41 (dd, *J* = 24.3, 12.1 Hz, 2H), 1.31 – 1.21 (m, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 197.0, 175.7, 136.5, 133.9, 129.0, 128.2, 76.3, 63.9, 43.3, 37.1, 33.3, 29.1, 25.8, 25.6; **FT-IR (thin film):** 1724, 1685, 1552, 1449, 1367, 1175, 1034, 998, 754, 688 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{18}H_{24}NO_5$ $[M+H]^+$ 334.1649; found: 334.1650; The ee value 94% (t_{minor} = 15.5 min, t_{major} = 20.3 min) was determined by HPLC analysis using Daicel Chiralpak ID with hexane/^{i}PrOH (80:20) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^{o}C.

(S)-2-(nitromethyl)-4-oxo-4-phenylbutyl pentanoate (3z'''')



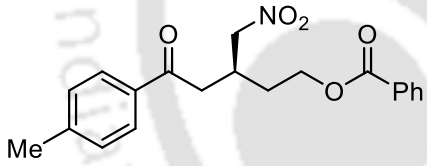
This compound was prepared according to the general procedure D. Reaction was completed after 4 d. Analytical TLC on silica gel using 12% ethyl acetate/hexane. Colorless oil (19 mg, 62% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.95 (d, *J* = 7.3 Hz, 2H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.8 Hz, 2H), 4.62 (d, *J* = 6.0 Hz, 2H), 4.23 (qd, *J* = 11.5, 5.6 Hz, 2H), 3.26 (dt, *J* = 11.9, 6.1 Hz, 1H), 3.19 (d, *J* = 6.5 Hz, 2H), 2.31 (t, *J* = 7.6 Hz, 2H), 1.61 (d, *J* = 7.5 Hz, 1H), 1.57 (d, *J* = 7.6 Hz, 1H), 1.37 – 1.30 (m, 2H), 0.91 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 196.9, 173.5, 136.6, 133.9, 129.0, 128.2, 76.3, 64.1, 37.2, 33.9, 33.3, 27.1, 22.4, 13.8; **FT-IR (thin film):** 1738, 1686, 1554, 1381, 1173, 1109, 1002, 755, 690 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{16}H_{22}NO_5$ $[M+H]^+$ 308.1492; found: 308.1493; The ee value 94% (t_{minor} = 15.0 min, t_{major} = 17.0 min) was determined by HPLC analysis using Daicel Chiralpak ID with hexane/^{i}PrOH (80:20) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^{o}C.

(S)-3-(nitromethyl)-5-oxo-5-phenylpentyl benzoate (5a)



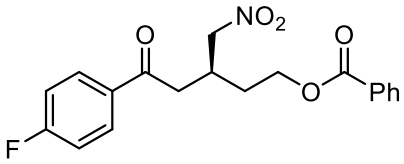
This compound was prepared according to the general procedure D. Reaction was completed after 5 d. Analytical TLC on silica gel using 10% ethyl acetate/hexane. Yellow oil (24 mg, 70% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.01 (d, *J* = 7.3 Hz, 2H), 7.94 (d, *J* = 7.4 Hz, 2H), 7.60 – 7.55 (m, 2H), 7.46 (t, *J* = 7.8 Hz, 2H), 7.43 (t, *J* = 7.8 Hz, 2H), 4.71 – 4.64 (m, 2H), 4.51 – 4.42 (m, 2H), 3.30 (dd, *J* = 18.1, 7.2 Hz, 1H), 3.19 (dd, *J* = 18.0, 5.5 Hz, 1H), 3.10 (dt, *J* = 12.2, 6.1 Hz, 1H), 2.04 (q, *J* = 6.4 Hz, 2H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 197.7, 166.6, 136.6, 133.8, 133.4, 129.9, 129.8, 128.9, 128.7, 128.2, 78.5, 62.3, 39.6, 30.9, 30.7; **FT-IR (thin film):** 1718, 1684, 1551, 1449, 1377, 1273, 1116, 753, 715 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{19}H_{20}NO_5$ $[M+H]^+$ 342.1336; found: 342.1335; The ee value 86% (t_{minor} = 28.0 min, t_{major} = 29.6 min) was determined by HPLC analysis using Daicel Chiralpak ID with hexane/^{i}PrOH (80:20) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C.

(S)-3-(nitromethyl)-5-oxo-5-(p-tolyl)pentyl benzoate (5b)



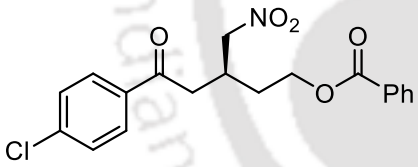
This compound was prepared according to the general procedure D. Reaction was completed after 5 d. Analytical TLC on silica gel using 10% ethyl acetate/hexane. Yellow oil (19 mg, 54% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.00 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.84 (d, *J* = 8.2 Hz, 2H), 7.58 – 7.54 (m, 1H), 7.43 (t, *J* = 7.8 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 4.66 (qd, *J* = 12.4, 5.7 Hz, 2H), 4.50 – 4.41 (m, 2H), 3.26 (dd, *J* = 17.9, 7.2 Hz, 1H), 3.16 (dd, *J* = 17.9, 5.5 Hz, 1H), 3.11 – 3.06 (m, 1H), 2.41 (s, 3H), 2.05 – 2.00 (m, 2H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 197.4, 166.7, 144.7, 134.2, 133.3, 130.0, 129.8, 129.6, 128.6, 128.3, 78.5, 62.3, 39.5, 31.0, 30.7, 21.9; **FT-IR (thin film):** 1717, 1681, 1606, 1550, 1378, 1274, 1113, 809, 713 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{120}H_{22}NO_5$ $[M+H]^+$ 356.1492; found: 356.1491; The ee value 93% (t_{minor} = 41.9 min, t_{major} = 45.0 min) was determined by HPLC analysis using Daicel Chiralpak ID with hexane/^{i}PrOH (85:15) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C.

(S)-5-(4-fluorophenyl)-3-(nitromethyl)-5-oxopentyl benzoate (5c)



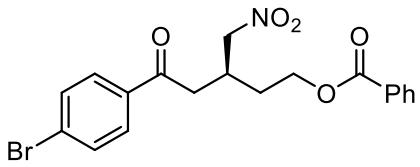
This compound was prepared according to the general procedure D. Reaction was completed after 5 d. Analytical TLC on silica gel using 10% ethyl acetate/hexane. Gummy oil (21 mg, 58% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.00 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.96 (dd, *J* = 8.9, 5.3 Hz, 2H), 7.59 – 7.55 (m, 1H), 7.43 (t, *J* = 7.8 Hz, 2H), 7.12 (t, *J* = 8.6 Hz, 2H), 4.70 – 4.64 (m, 2H), 4.50 – 4.41 (m, 2H), 3.26 (dd, *J* = 17.9, 7.1 Hz, 1H), 3.15 (dd, *J* = 17.9, 5.5 Hz, 1H), 3.08 (td, *J* = 11.5, 5.7 Hz, 1H), 2.03 (td, *J* = 6.9, 1.4 Hz, 2H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 196.1, 166.9 (d, *J* = 63.0 Hz), 165.4, 133.4, 133.1 (d, *J* = 3.0 Hz), 130.9 (d, *J* = 9.0 Hz),, 129.9, 129.8, 128.7, 116.1 (d, *J* = 21.0 Hz), 78.4, 62.2, 39.5, 30.9, 30.7; **FT-IR (thin film):** 1718, 1685, 1599, 1551, 1378, 1275, 1156, 1114, 835, 714 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{19}H_{19}NFO_5$ $[M+H]^+$ 360.1242; found: 360.1243; The ee value 88% (t_{minor} = 34.6 min, t_{major} = 29.4 min) was determined by HPLC analysis using Daicel Chiralpak IB with hexane/^{i}PrOH (93:7) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^{o}C.

(S)-5-(4-chlorophenyl)-3-(nitromethyl)-5-oxopentyl benzoate (5d)



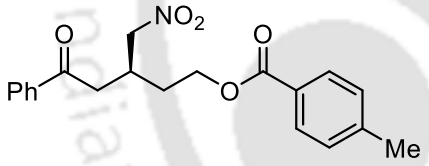
This compound was prepared according to the general procedure D. Reaction was completed after 5 d. Analytical TLC on silica gel using 10% ethyl acetate/hexane. Gummy oil (24 mg, 64% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.99 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.87 (d, *J* = 8.7 Hz, 2H), 7.58 – 7.55 (m, 1H), 7.42 (dt, *J* = 7.6, 3.5 Hz, 4H), 4.70 – 4.63 (m, 2H), 4.50 – 4.42 (m, 2H), 3.26 (dd, *J* = 18.0, 7.1 Hz, 1H), 3.15 (dd, *J* = 18.0, 5.6 Hz, 1H), 3.10 – 3.05 (m, 1H), 2.03 (td, *J* = 6.9, 1.7 Hz, 2H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 196.5, 166.6, 140.3, 134.9, 133.4, 129.9, 129.7, 129.6, 129.3, 128.6, 78.4, 62.2, 39.6, 30.9, 30.6; **FT-IR (thin film):** 1717, 1685, 1589, 1550, 1379, 1274, 1096, 1003, 820, 713 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{19}H_{19}NClO_5$ $[M+H]^+$ 376.0946; found: 376.0949; The ee value 91% (t_{minor} = 31.1 min, t_{major} = 38.7 min) was determined by HPLC analysis using Daicel Chiralpak ID with hexane/^{i}PrOH (85:15) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^{o}C.

(S)-5-(4-bromophenyl)-3-(nitromethyl)-5-oxopentyl benzoate (5e)



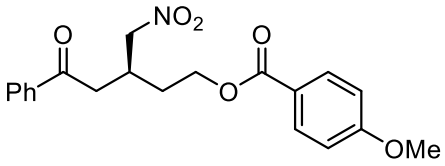
This compound was prepared according to the general procedure D. Reaction was completed after 5 d. Analytical TLC on silica gel using 10% ethyl acetate/hexane. Yellow oil (28 mg, 67% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.99 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.79 (d, *J* = 8.6 Hz, 2H), 7.61 – 7.54 (m, 3H), 7.43 (t, *J* = 7.8 Hz, 2H), 4.69 – 4.63 (m, 2H), 4.50 – 4.41 (m, 2H), 3.25 (dd, *J* = 18.0, 7.1 Hz, 1H), 3.14 (dd, *J* = 18.0, 5.6 Hz, 1H), 3.10 – 3.04 (m, 1H), 2.03 (td, *J* = 6.8, 1.8 Hz, 2H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 196.7, 166.6, 135.3, 133.4, 132.3, 129.9, 129.7, 129.7, 129.1, 128.6, 78.3, 62.2, 39.6, 30.9, 30.6; **FT-IR (thin film):** 1717, 1686, 1585, 1550, 1381, 1274, 1113, 1070, 1003, 815, 713 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{19}H_{19}NBrO_5$ $[M+H]^+$ 420.0441; found: 420.0440; The ee value 91% (t_{minor} = 34.8 min, t_{major} = 46.7 min) was determined by HPLC analysis using Daicel Chiralpak ID with hexane/^{i}PrOH (85:15) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^{o}C.

(S)-3-(nitromethyl)-5-oxo-5-phenylpentyl 4-methylbenzoate (5f)



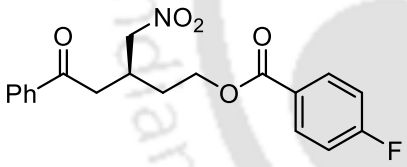
This compound was prepared according to the general procedure D. Reaction was completed after 5 d. Analytical TLC on silica gel using 10% ethyl acetate/hexane. Pale yellow oil (18 mg, 51% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.94 (d, *J* = 7.1 Hz, 2H), 7.89 (d, *J* = 8.2 Hz, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 4.70 – 4.64 (m, 2H), 4.48 – 4.40 (m, 2H), 3.29 (dd, *J* = 18.0, 7.2 Hz, 1H), 3.19 (dd, *J* = 18.1, 5.5 Hz, 1H), 3.09 (dt, *J* = 11.9, 6.0 Hz, 1H), 2.41 (s, 3H), 2.04 – 2.01 (m, 2H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 197.7, 166.7, 144.1, 136.6, 133.8, 129.8, 129.4, 128.9, 128.2, 127.2, 78.5, 62.1, 39.6, 31.0, 30.7, 21.9; **FT-IR (thin film):** 1714, 1685, 1609, 1550, 1377, 1275, 1108, 753, 690 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{20}H_{22}NO_5$ $[M+H]^+$ 356.1492; found: 356.1494; The ee value 88% (t_{minor} = 32.7 min, t_{major} = 35.8 min) was determined by HPLC analysis using Daicel Chiralpak IA with hexane/^{i}PrOH (95:5) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^{o}C.

(S)-3-(nitromethyl)-5-oxo-5-phenylpentyl 4-methoxybenzoate (5g)



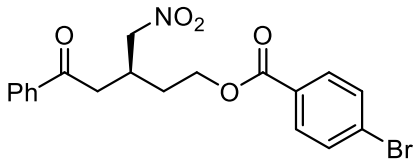
This compound was prepared according to the general procedure D. Reaction was completed after 5 d. Analytical TLC on silica gel using 18% ethyl acetate/hexane. Sticky oil (18 mg, 48% yield); **^{1}H NMR (600 MHz, CDCl3):** δ 8.00 – 7.93 (m, 4H), 7.63 – 7.59 (m, 1H), 7.49 (t, *J* = 7.8 Hz, 2H), 6.92 (d, *J* = 8.9 Hz, 2H), 4.72 – 4.66 (m, 2H), 4.46 (ddt, *J* = 17.5, 11.6, 5.9 Hz, 2H), 3.88 (s, 3H), 3.31 (dd, *J* = 18.0, 7.2 Hz, 1H), 3.21 (dd, *J* = 18.0, 5.5 Hz, 1H), 3.11 (dt, *J* = 12.7, 6.2 Hz, 1H), 2.04 (q, *J* = 6.3 Hz, 2H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 197.7, 166.4, 163.7, 136.6, 133.8, 131.8, 128.9, 128.2, 122.4, 113.9, 78.5,.61.9, 55.6, 39.6, 31.0, 30.7; **FT-IR (thin film):** 1710, 1685, 1604, 1550, 1511, 1378, 1259, 1169, 1105, 1027, 849, 769, 692 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{20}H_{22}NO_6$ $[M+H]^+$ 372.1442; found: 372.1445; The ee value 92% (t_{minor} = 52.9 min, t_{major} = 55.8 min) was determined by HPLC analysis using Daicel Chiralpak ID with hexane/^{i}PrOH (80:20) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^{o}C.

(S)-3-(nitromethyl)-5-oxo-5-phenylpentyl 4-fluorobenzoate (5h)



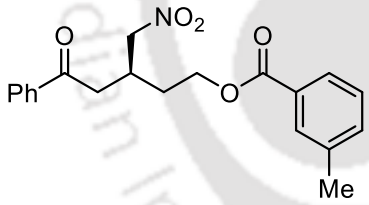
This compound was prepared according to the general procedure D. Reaction was completed after 5 d. Analytical TLC on silica gel using 12% ethyl acetate/hexane. Pale yellow oil (16 mg, 45% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.02 (dd, *J* = 8.9, 5.4 Hz, 2H), 7.94 (dd, *J* = 8.3, 1.1 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 2H), 7.09 (t, *J* = 8.7 Hz, 2H), 4.66 (qd, *J* = 12.4, 5.7 Hz, 2H), 4.49 – 4.41 (m, 2H), 3.29 (dd, *J* = 18.0, 7.1 Hz, 1H), 3.18 (dd, *J* = 18.0, 5.6 Hz, 1H), 3.09 (dt, *J* = 12.6, 5.8 Hz, 1H), 2.03 (dd, *J* = 12.9, 6.4 Hz, 2H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 197.6, 166.9, 165.5 (d, *J* = 54.0 Hz), 136.6, 133.9, 132.4 (d, *J* = 9.0 Hz), 129.0, 128.2, 115.8 (d, *J* = 22.5 Hz), 78.5, 62.4, 39.7, 30.9, 30.7; **FT-IR (thin film):** 1718, 1684, 1603, 1551, 1380, 1275, 1115, 767, 689 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{19}H_{22}N_2FO_5$ $[M+NH_4]^+$ 377.1507; found: 377.1509; found: 224.0921; The ee value 92% (t_{minor} = 45.6 min, t_{major} = 52.9 min) was determined by HPLC analysis using Daicel Chiralpak IA with hexane/^{i}PrOH (95:5) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^{o}C.

(S)-3-(nitromethyl)-5-oxo-5-phenylpentyl 4-bromobenzoate (5i)



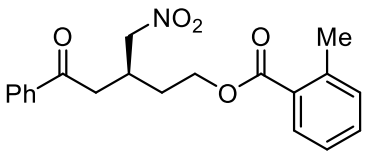
This compound was prepared according to the general procedure D. Reaction was completed after 5 d. Analytical TLC on silica gel using 12% ethyl acetate/hexane. Pale yellow oil (18 mg, 43% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.93 (d, *J* = 7.2 Hz, 2H), 7.85 (d, *J* = 8.6 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.56 (d, *J* = 8.6 Hz, 2H), 7.47 (t, *J* = 7.8 Hz, 2H), 4.66 (qd, *J* = 12.4, 5.7 Hz, 2H), 4.45 (ddt, *J* = 17.7, 11.6, 5.8 Hz, 2H), 3.29 (dd, *J* = 18.0, 7.0 Hz, 1H), 3.18 (dd, *J* = 18.0, 5.6 Hz, 1H), 3.08 (dt, *J* = 12.5, 5.8 Hz, 1H), 2.03 (dd, *J* = 12.9, 6.3 Hz, 2H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 197.6, 165.9, 136.6, 133.9, 132.0, 131.3, 129.0, 128.8, 128.5, 128.2, 78.5, 62.5, 39.7, 30.9, 30.6; **FT-IR (thin film):** 1719, 1685, 1590, 1550, 1380, 1272, 1103, 1012, 756, 689 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{19}H_{22}N_2BrO_5$ $[M+NH_4]^+$ 437.0707; found: 437.0697; The ee value 89% (t_{minor} = 38.5 min, t_{major} = 43.1 min) was determined by HPLC analysis using Daicel Chiralpak IA with hexane/^{i}PrOH (95:5) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^{o}C.

(S)-3-(nitromethyl)-5-oxo-5-phenylpentyl 3-methylbenzoate (5j)



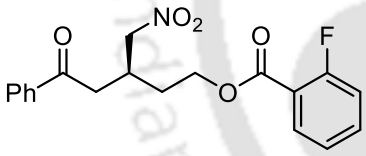
This compound was prepared according to the general procedure D. Reaction was completed after 5 d. Analytical TLC on silica gel using 10% ethyl acetate/hexane. Pale yellow oil (19 mg, 53% yield); **^{1}H NMR (600 MHz, CDCl3):** δ 7.94 (dd, *J* = 8.3, 1.1 Hz, 2H), 7.83 – 7.79 (m, 2H), 7.60 – 7.56 (m, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 7.37 (d, *J* = 7.6 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 4.70 – 4.63 (m, 2H), 4.45 (dtd, *J* = 17.8, 11.6, 5.8 Hz, 2H), 3.29 (dd, *J* = 18.1, 7.3 Hz, 1H), 3.20 (dd, *J* = 18.0, 5.5 Hz, 1H), 3.09 (td, *J* = 11.7, 5.8 Hz, 1H), 2.39 (s, 3H), 2.04 (q, *J* = 6.4 Hz, 2H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 197.8, 166.8, 138.5, 136.7, 134.2, 133.8, 130.3, 129.9, 129.8, 129.0, 128.7, 128.6, 128.2, 126.9, 78.5, 62.3, 39.6, 31.0, 30.7, 21.5; **FT-IR (thin film):** 1716, 1685, 1550, 1378, 1278, 1200, 1109, 748, 689 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{20}H_{22}NO_5$ $[M+H]^+$ 356.1492; found: 356.1493; The ee value 94% (t_{minor} = 47.1 min, t_{major} = 53.5 min) was determined by HPLC analysis using Daicel Chiralpak IA with hexane/^{i}PrOH (97.5:2.5) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^{o}C.

(S)-3-(nitromethyl)-5-oxo-5-phenylpentyl 2-methylbenzoate (5k)



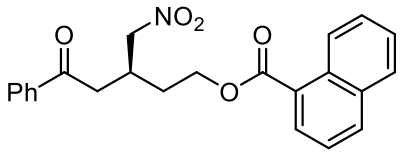
This compound was prepared according to the general procedure D. Reaction was completed after 5 d. Analytical TLC on silica gel using 10% ethyl acetate/hexane. Pale yellow oil (20 mg, 56% yield); **^{1}H NMR (600 MHz, CDCl3):** δ 7.94 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.87 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.60 – 7.56 (m, 1H), 7.46 (dd, *J* = 8.1, 7.5 Hz, 2H), 7.40 (td, *J* = 7.5, 1.4 Hz, 1H), 7.23 (dd, *J* = 15.9, 7.8 Hz, 2H), 4.70 – 4.63 (m, 2H), 4.47 – 4.39 (m, 2H), 3.29 (dd, *J* = 18.0, 7.2 Hz, 1H), 3.19 (dd, *J* = 18.0, 5.5 Hz, 1H), 3.08 (qd, *J* = 6.8, 1.1 Hz, 1H), 2.59 (s, 3H), 2.02 (dt, *J* = 6.8, 3.5 Hz, 2H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 197.7, 167.5, 140.6, 136.6, 133.8, 132.4, 131.9, 130.7, 129.3, 128.9, 128.2, 126.0, 78.5, 61.9, 39.6, 30.9, 30.7, 21.9; **FT-IR (thin film):** 1716, 1685, 1551, 1378, 1255, 1082, 742, 691 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{20}H_{22}NO_5$ $[M+H]^+$ 356.1492; found: 356.1495; The ee value 94% (t_{minor} = 21.4 min, t_{major} = 24.2 min) was determined by HPLC analysis using Daicel Chiralpak IA with hexane/^{i}PrOH (95:5) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^{o}C.

(S)-3-(nitromethyl)-5-oxo-5-phenylpentyl 2-fluorobenzoate (5l)



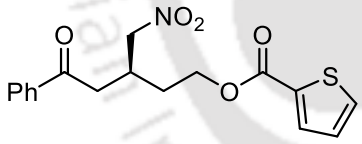
This compound was prepared according to the general procedure D. Reaction was completed after 5 d. Analytical TLC on silica gel using 12% ethyl acetate/hexane. Colorless oil (15 mg, 42% yield); **^{1}H NMR (600 MHz, CDCl3):** δ 7.99 – 7.92 (m, 3H), 7.62 – 7.58 (m, 1H), 7.57 – 7.53 (m, 1H), 7.48 (t, *J* = 7.8 Hz, 2H), 7.23 (td, *J* = 7.7, 1.0 Hz, 1H), 7.14 (ddd, *J* = 10.9, 8.4, 0.9 Hz, 1H), 4.71 (d, *J* = 5.7 Hz, 2H), 4.54 – 4.47 (m, 2H), 3.32 (dd, *J* = 18.0, 7.1 Hz, 1H), 3.23 (dd, *J* = 18.0, 5.6 Hz, 1H), 3.15 – 3.10 (m, 1H), 2.06 (dd, *J* = 12.9, 6.4 Hz, 2H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 197.8, 164.5 (d, *J* = 4.5 Hz), 162.9, 161.2, 136.6, 135.0 (d, *J* = 9.0 Hz), 133.8, 132.4, 128.9, 128.2, 124.3 (d, *J* = 4,5 Hz), 117.3 (d, *J* = 21.0 Hz), 78.4, 62.8, 39.6, 31.1, 30.6; **FT-IR (thin film):** 1723, 1685, 1613, 1550, 1454, 1380, 1298, 1254, 1127, 1084, 757, 691 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{19}H_{22}N_2FO_5$ $[M+NH_4]^+$ 377.1507; found: 377.1503; The ee value 92% (t_{minor} = 31.2 min, t_{major} = 38.5 min) was determined by HPLC analysis using Daicel Chiralpak IA with hexane/^{i}PrOH (95:5) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^{o}C.

(S)-3-(nitromethyl)-5-oxo-5-phenylpentyl 1-naphthoate (5m)



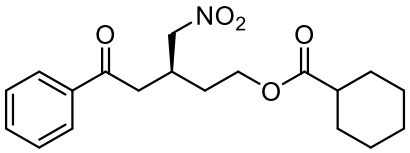
This compound was prepared according to the general procedure D. Reaction was completed after 5 d. Analytical TLC on silica gel using 12% ethyl acetate/hexane. Sticky oil (22 mg, 56% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.89 (d, *J* = 8.7 Hz, 1H), 8.15 (dd, *J* = 7.3, 1.2 Hz, 1H), 8.02 (d, *J* = 8.2 Hz, 1H), 7.94 – 7.87 (m, 3H), 7.62 (ddd, *J* = 8.5, 6.8, 1.4 Hz, 1H), 7.58 – 7.52 (m, 2H), 7.49 – 7.45 (m, 1H), 7.43 (t, *J* = 7.8 Hz, 2H), 4.72 – 4.65 (m, 2H), 4.59 – 4.51 (m, 2H), 3.30 (dd, *J* = 18.0, 7.1 Hz, 1H), 3.22 (dd, *J* = 18.0, 5.5 Hz, 1H), 3.14 (td, *J* = 11.7, 5.9 Hz, 1H), 2.09 (q, *J* = 6.4 Hz, 2H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 197.7, 167.5, 136.6, 134.0, 133.9, 133.8, 131.5, 130.5, 128.9, 128.8, 128.2, 128.1, 126.8, 126.5, 125.8, 124.7, 78.5, 62.3, 39.7, 31.0, 30.7; **FT-IR (thin film):** 1712, 1684, 1549, 1377, 1242, 1196, 1135, 1004, 784, 752, 690 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{23}H_{25}N_2O_5$ $[M+NH_4]^+$ 409.1758; found: 409.1756; The ee value 96% (t_{minor} = 36.1 min, t_{major} = 31.4 min) was determined by HPLC analysis using Daicel Chiralpak ID with hexane/^{i}PrOH (80:20) as the eluent, flow: 1.0 mL/min, 220 nm, 25 ^{o}C.

(S)-3-(nitromethyl)-5-oxo-5-phenylpentyl thiophene-2-carboxylate (5n)



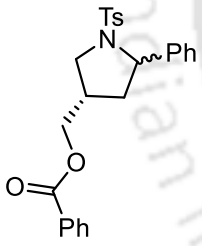
This compound was prepared according to the general procedure D. Reaction was completed after 5 d. Analytical TLC on silica gel using 12% ethyl acetate/hexane. Sticky oil (17 mg, 49% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.94 (d, *J* = 7.2 Hz, 2H), 7.79 (dd, *J* = 3.7, 1.2 Hz, 1H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.56 (dd, *J* = 5.0, 1.2 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 2H), 7.10 (dd, *J* = 4.9, 3.8 Hz, 1H), 4.71 – 4.63 (m, 2H), 4.48 – 4.39 (m, 2H), 3.29 (dd, *J* = 18.0, 7.2 Hz, 1H), 3.19 (dd, *J* = 18.0, 5.5 Hz, 1H), 3.07 (dt, *J* = 12.0, 6.0 Hz, 1H), 2.02 (td, *J* = 6.8, 1.5 Hz, 2H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 197.7, 162.2, 136.6, 133.9, 133.8, 133.4, 132.3, 128.9, 128.2, 128.1, 78.4, 62.5, 39.6, 31.0, 30.6; **FT-IR (thin film):** 1707, 1549, 1419, 1364, 1264, 1095, 759, 691 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{17}H_{21}N_2SO_5$ $[M+NH_4]^+$ 365.1166; found: 365.1165; The ee value 94% (t_{minor} = 34.7 min, t_{major} = 37.6 min) was determined by HPLC analysis using Daicel Chiralpak IA with hexane/^{i}PrOH (95:5) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^{o}C.

(S)-3-(nitromethyl)-5-oxo-5-phenylpentyl cyclohexanecarboxylate (5o)



This compound was prepared according to the general procedure D. Reaction was completed after 5 d. Analytical TLC on silica gel using 10% ethyl acetate/hexane. Sticky oil (18 mg, 52% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.95 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 2H), 4.65 – 4.58 (m, 2H), 4.24 – 4.15 (m, 2H), 3.25 (dd, *J* = 18.0, 7.1 Hz, 1H), 3.13 (dd, *J* = 18.0, 5.5 Hz, 1H), 3.01 – 2.95 (m, 1H), 2.24 (tt, *J* = 11.4, 3.6 Hz, 1H), 1.92 – 1.87 (m, 3H), 1.73 (dd, *J* = 9.4, 3.6 Hz, 2H), 1.63 (dd, *J* = 10.2, 4.2 Hz, 1H), 1.40 (q, *J* = 12.7 Hz, 2H), 1.27 – 1.15 (m, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 197.7, 176.2, 136.7, 133.8, 128.9, 128.2, 78.4, 61.4, 43.3, 39.6, 30.9, 30.6, 29.2, 25.9, 25.6; **FT-IR (thin film):** 1728, 1686, 1551, 1449, 1367, 1246, 1170, 1133, 753, 691 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{19}H_{29}N_2O_5$ $[M+NH_4]^+$ 365.2071; found: 365.2073; The ee value 92% (t_{minor} = 17.3 min, t_{major} = 23.6 min) was determined by HPLC analysis using Daicel Chiralpak IA with hexane/^{i}PrOH (95:5) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C.

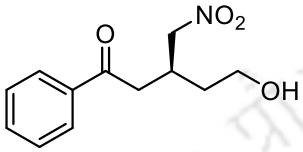
(*(S)-(5-phenyl-1-tosylpyrrolidin-3-yl)methyl benzoate (7)*



This compound was prepared according to the general procedure D. Analytical TLC on silica gel using 10% ethyl acetate/hexane. White solid (26.5 mg, 61% yield); **Mp:** 126-128 °C; Diastereomeric ratio = 1.5:1); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.97 (d, *J* = 7.3 Hz, 2H), 7.95 (d, *J* = 7.4 Hz, 1H), 7.68 (d, *J* = 8.1 Hz, 1H), 7.59 (t, *J* = 7.2 Hz, 3H), 7.44 (t, *J* = 7.7 Hz, 3H), 7.35 – 7.31 (m, 3H), 7.30 – 7.27 (m, 3H), 7.24 (d, *J* = 7.8 Hz, 4H), 4.90 (dd, *J* = 8.2, 2.8 Hz, 1H), 4.72 (t, *J* = 8.1 Hz, 1H), 4.28 (dd, *J* = 11.1, 5.9 Hz, 1H), 4.18 (dd, *J* = 10.9, 6.9 Hz, 2H), 3.96 – 3.92 (m, 1H), 3.87 (dd, *J* = 10.0, 7.2 Hz, 1H), 3.46 – 3.40 (m, 1H), 3.32 – 3.26 (m, 1H), 2.74 (dt, *J* = 14.8, 7.4 Hz, 1H), 2.49 – 2.43 (m, 1H), 2.41 (s, 3H), 2.40 (s, 2H), 2.36 (dd, *J* = 15.2, 8.1 Hz, 1H), 1.99 (ddd, *J* = 12.3, 6.1, 3.0 Hz, 1H), 1.86 (dd, *J* = 21.5, 9.2 Hz, 1H), 1.77 (dd, *J* = 22.0, 9.9 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 166.4, 166.3, 143.8, 143.7, 142.8, 142.3, 135.3, 134.7, 133.4, 129.89, 129.87, 129.8, 129.7, 128.68, 128.67, 128.65, 127.7, 127.6, 127.5, 126.6, 126.2, 65.4, 65.1, 64.2, 63.1, 52.8, 51.7, 40.2, 38.5, 38.0, 36.6, 21.8, 21.7; **FT-IR (thin film):** 1714, 1599, 1452, 1346, 1284, 1157, 11119, 816, 756, 708, 662, 590, 548 cm^{-1};

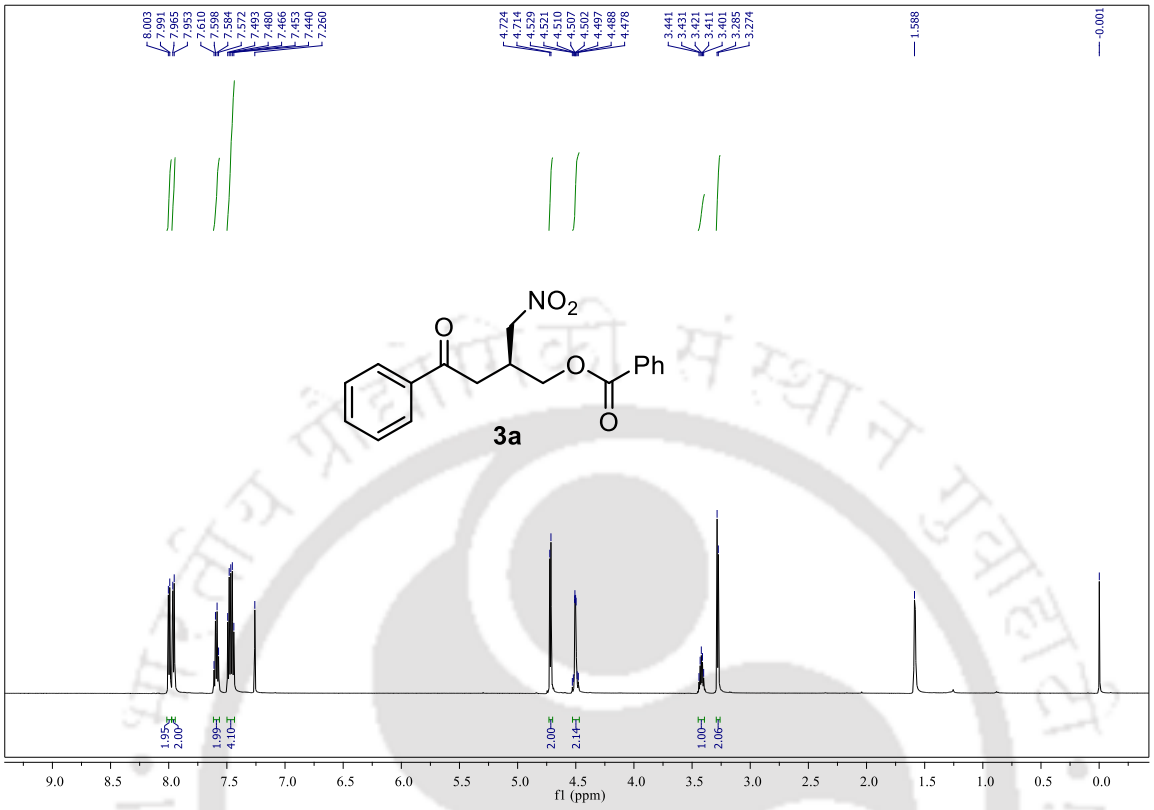
HRMS (+ESI): Calcd for $C_{25}H_{26}NSO_4$ $[M+H]^+$ 436.1577; found: 436.1570; The ee value for major diastereomer 99% (t_{minor} = 50.1 min, t_{major} = 45.6 min) and minor diastereomer 96% (t_{minor} = 53.3 min, t_{major} = 58.6 min) was determined by HPLC analysis using Daicel Chiralpak IA with hexane/^{i}PrOH (93:7) as the eluent, flow: 1.0 mL/min, 220 nm, 25 ^{o}C.

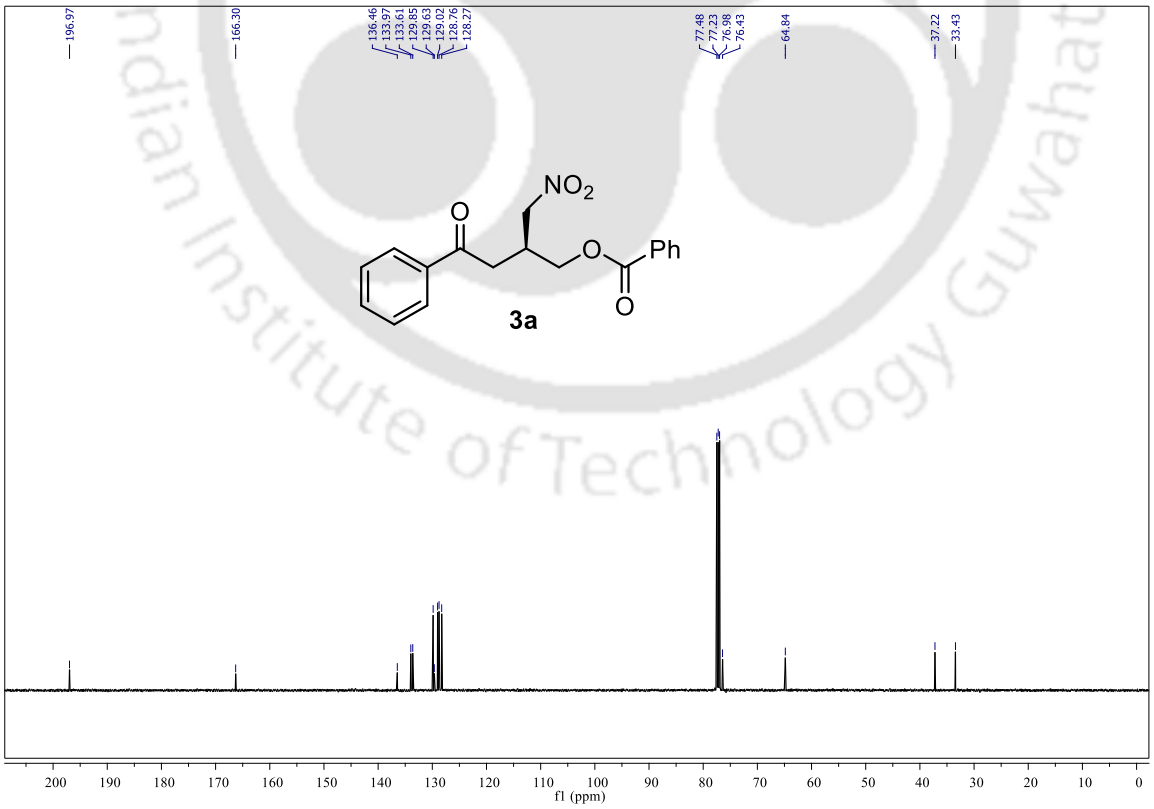
(S)-5-hydroxy-3-(nitromethyl)-1-phenylpentan-1-one (8)

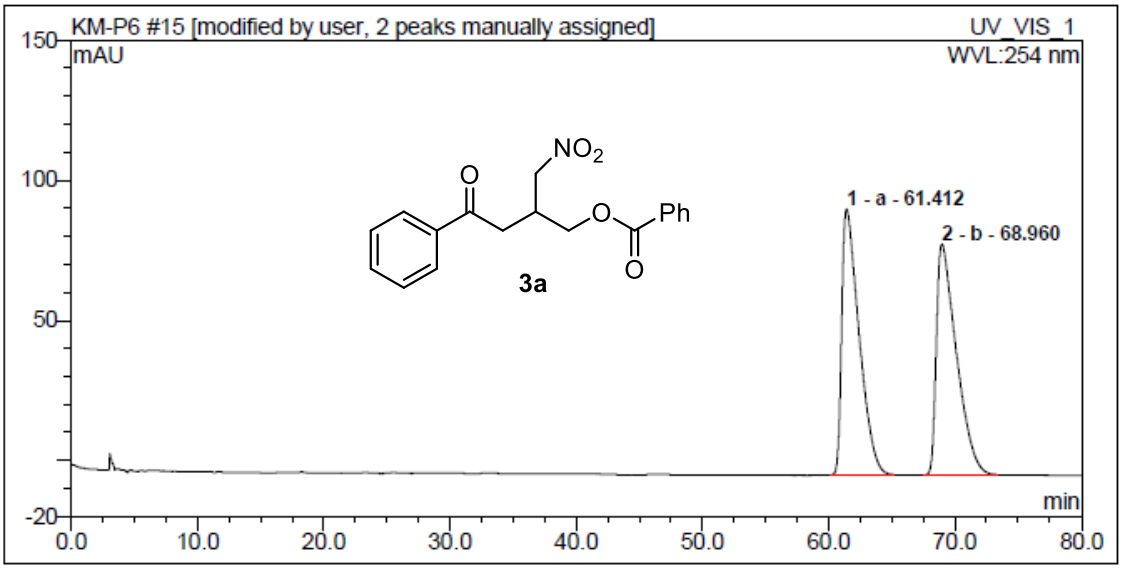


This compound was prepared according to the general procedure F. Analytical TLC on silica gel using 25% ethyl acetate/hexane. Sticky oil (13 mg, 58% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.96 (d, *J* = 7.1 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 2H), 4.65 (qd, *J* = 12.4, 6.2 Hz, 2H), 3.84 – 3.79 (m, 1H), 3.78 – 3.72 (m, 1H), 3.22 (dd, *J* = 17.7, 6.8 Hz, 1H), 3.15 (dd, *J* = 17.7, 6.2 Hz, 1H), 3.11 – 3.06 (m, 1H), 1.91 (s, 1H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 198.0, 136.6, 133.9, 129.0, 128.3, 76.4, 62.7, 37.1, 35.9; **FT-IR (thin film):** 3435, 1684, 1551, 1379, 1221, 1048, 756, 692 cm^{-1}; **HRMS (+ESI):** Calcd for $C_{11}H_{14}NO_4$ $[M+H]^+$ 224.0917; found: 224.0921; The ee value 95% (t_{minor} = 37.0 min, t_{major} = 31.7 min) was determined by HPLC analysis using Daicel Chiralpak IA with hexane/^{i}PrOH (93:7) as the eluent, flow: 1.0 mL/min, 220 nm, 25 ^{o}C.

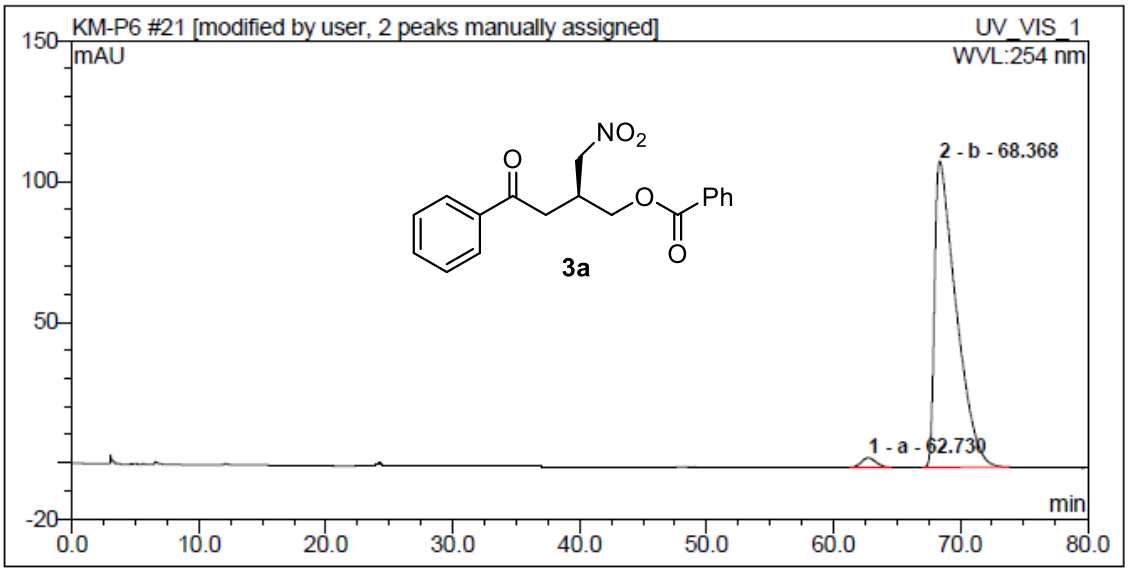
5.8 Selected NMR spectra and HPLC chromatogram



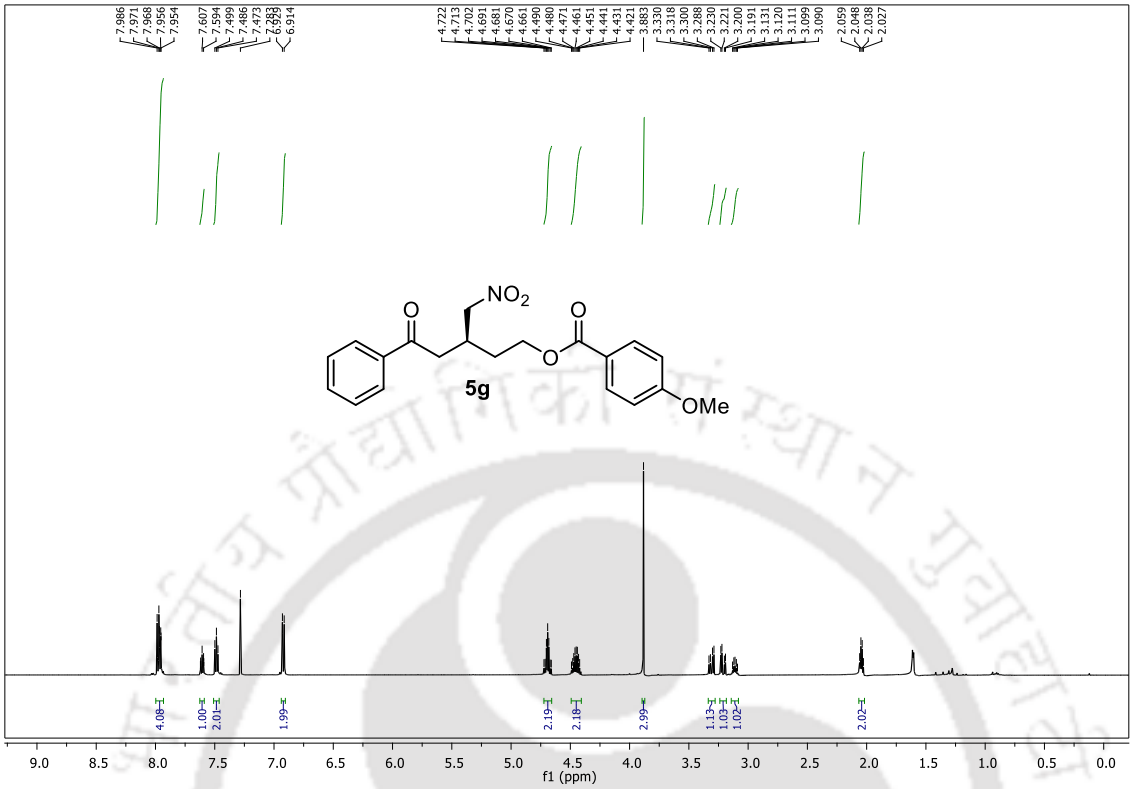


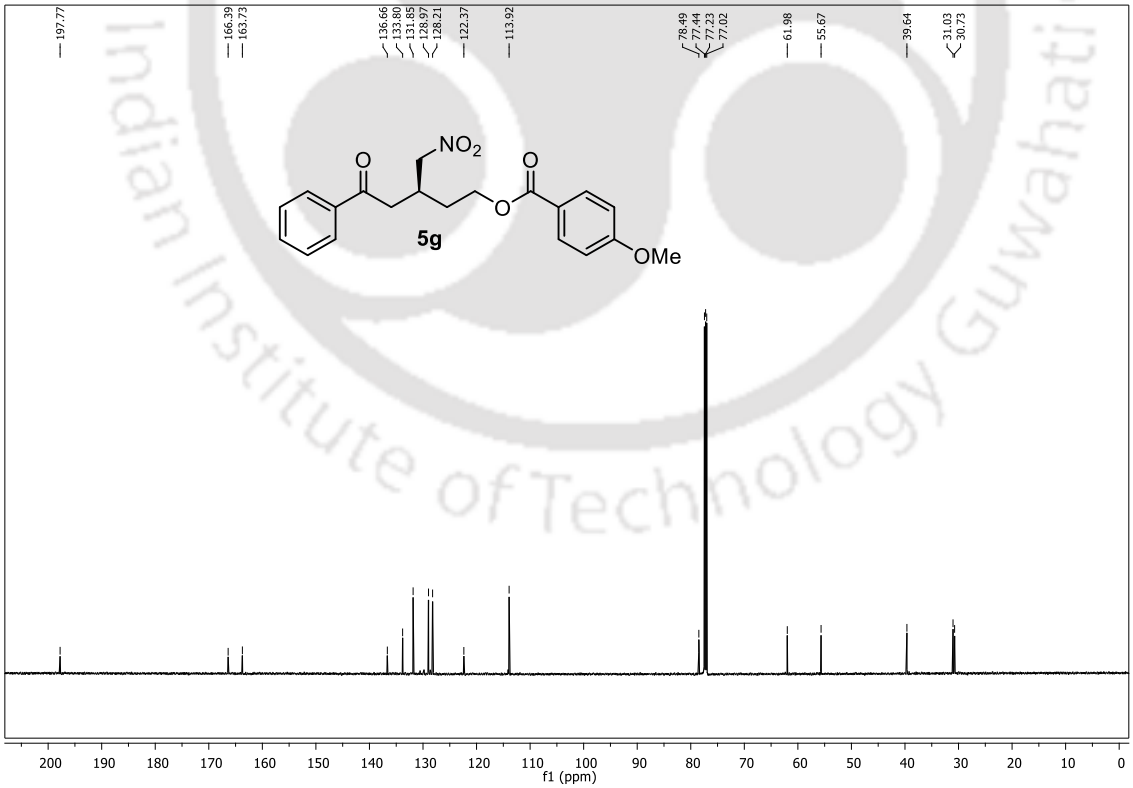


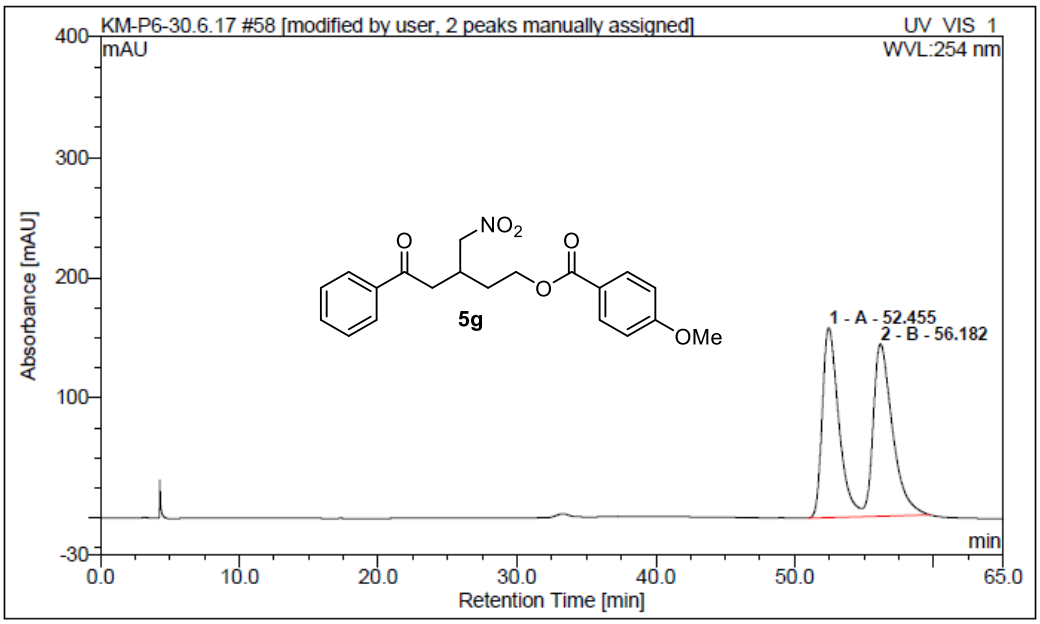
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	a	61.41	150.7643	49.94563378	94.8733	n.a.
2	b	68.96	151.093	50.05436622	82.407	n.a.



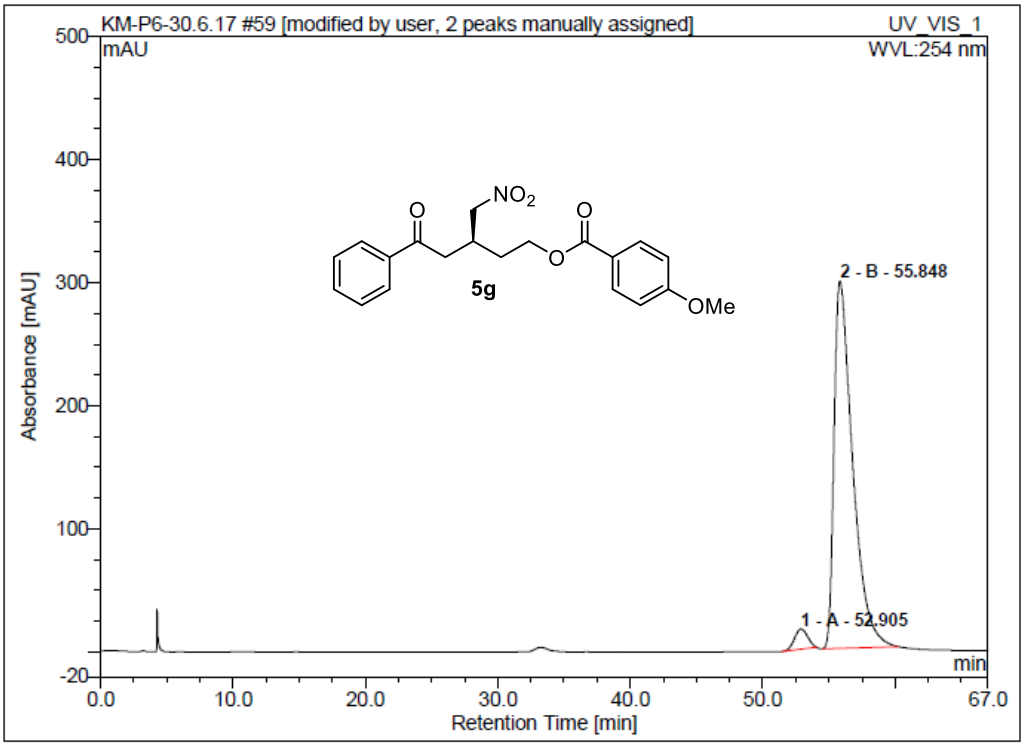
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	a	62.73	4.397907	2.012908635	3.36042	n.a.
2	b	68.37	214.087	97.98709136	108.868	n.a.



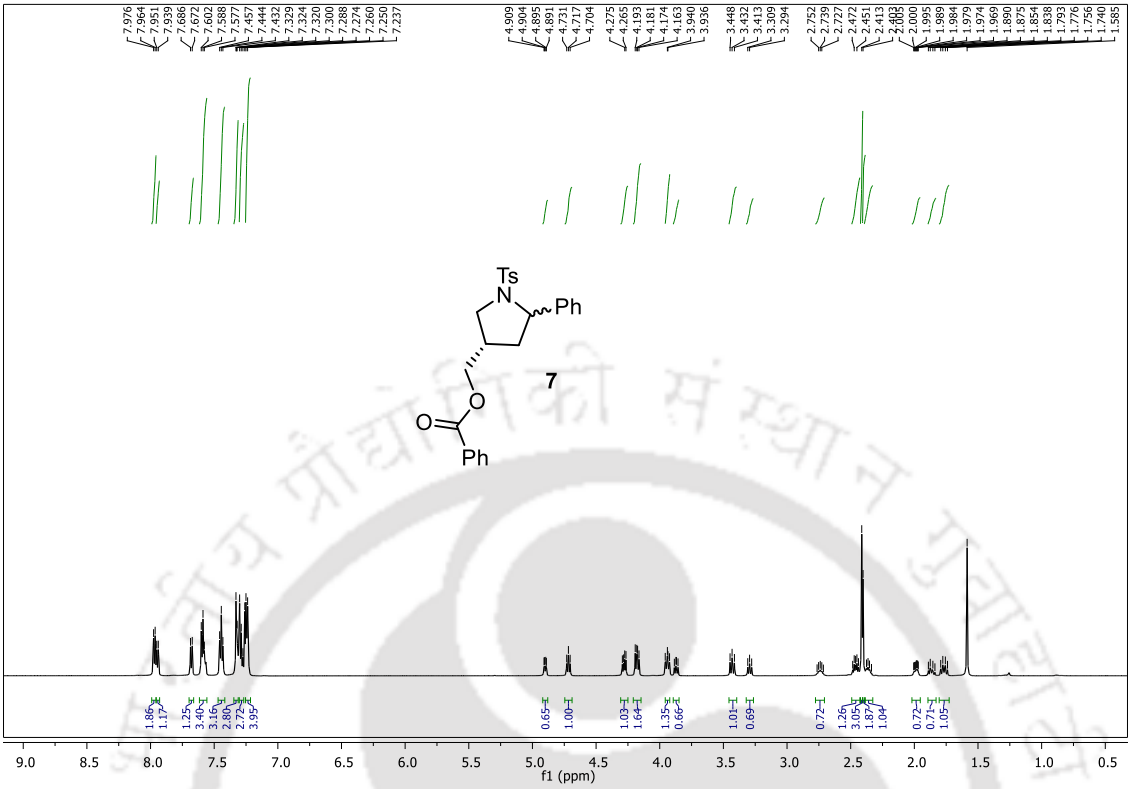


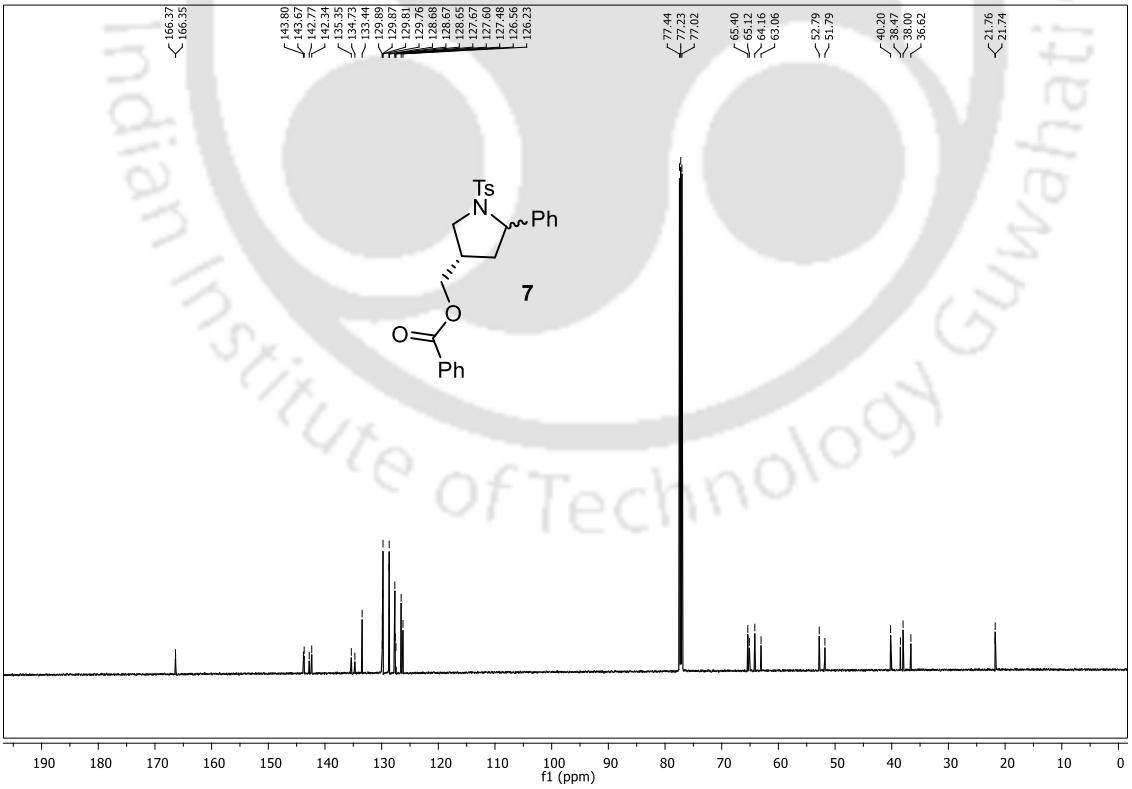


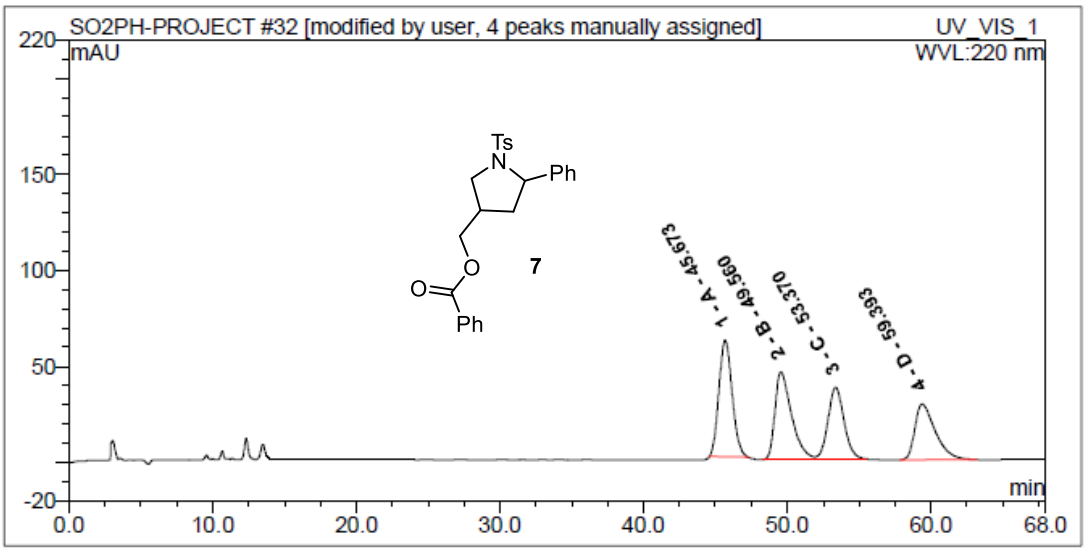
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	A	52.46	217.757	48.61045709	157.8221	n.a.
2	B	56.18	230.206	51.38954291	143.179	n.a.



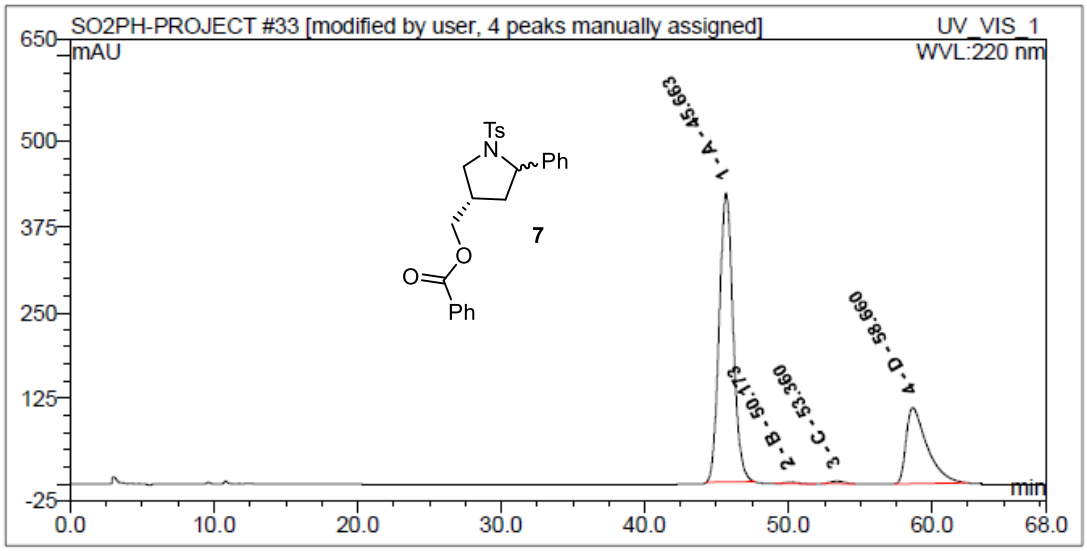
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	A	52.91	18.86732	3.739955263	16.46124	n.a.
2	B	55.85	485.612	96.26004474	298.312	n.a.





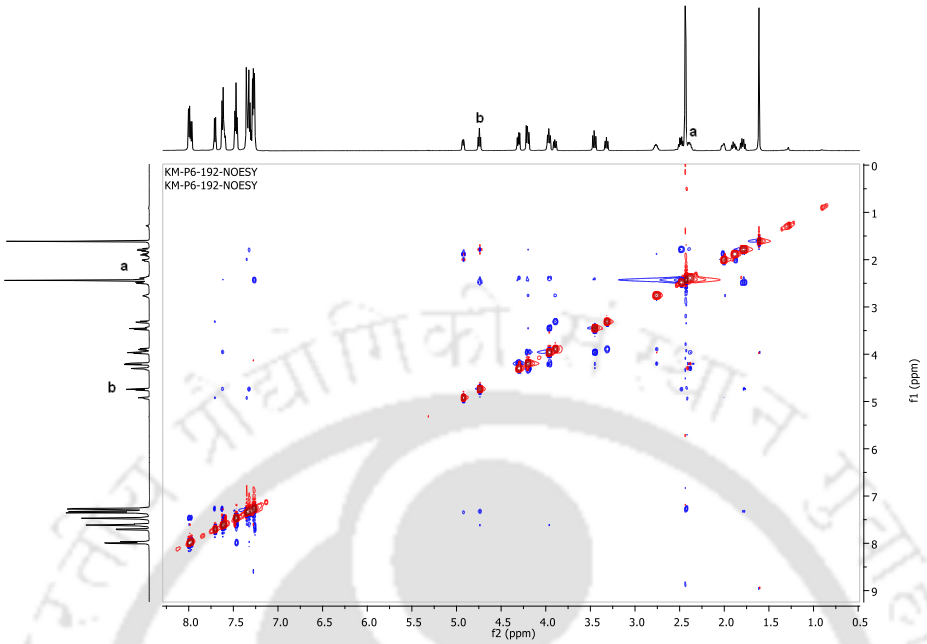


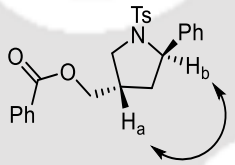
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	A	45.67	65.11313	29.37776264	60.81126	n.a.
2	B	49.56	60.99447	27.51950722	45.45578	n.a.
3	C	53.37	47.61418	21.48258272	37.1529	n.a.
4	D	59.39	47.919	21.62014742	29.072	n.a.



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	A	45.66	473.2161	71.03155511	422.5161	n.a.
2	B	50.17	2.228467	0.3345014562	1.95029	n.a.
3	C	53.36	3.982025	0.5977172566	3.58876	n.a.
4	D	58.66	186.779	28.03622617	110.753	n.a.

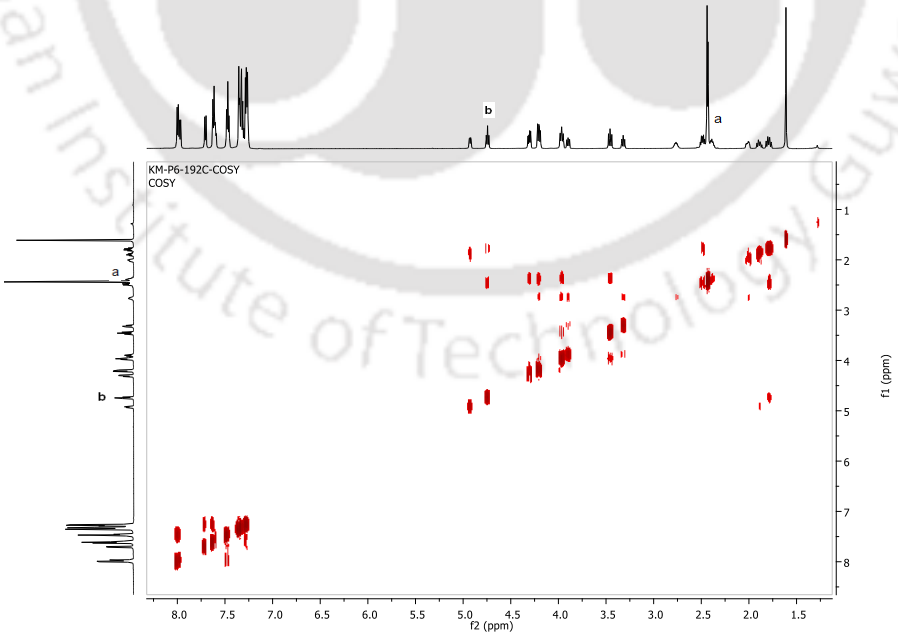
NOESY spectra of compound 7





7 No NOE

COSY spectra of compound 7



List of publications and presentations

1. Copper(I)-Catalyzed (*Z*)-*β*-(Tosyloxy)alkenyl Iodide Synthesis from (Aryl)[(*E*)-*β*-(tosyloxy)alkenyl]iodonium Tosylates: Diversity-Oriented Synthesis of Trisubstituted Alkenes, **Keshab Mondal** and Subhas Chandra Pan, *Eur. J. Org. Chem*. **2015**, 2129.
2. Organocatalytic Redox Isomerization of Electron-Deficient Allylic Alcohols: Synthesis of 1,4-ketoaldehydes, **Keshab Mondal**, Buddhadeb Mondal, and Subhas Chandra Pan, *J. Org. Chem*. **2016**, *81*, 4835.
3. Lewis Acid Catalyzed [3+3] Annulation of Donor–Acceptor Cyclopropanes with *γ*-Hydroxyenones: Access to Highly Functionalized Tetrahydropyrans, **Keshab Mondal** and Subhas Chandra Pan, *Eur. J. Org. Chem*. **2017**, 534.
4. Synthesis of 2,5-Disubstituted Furans from $Sc(OTf)_3$ Catalyzed Reaction of Aryl Oxiranediesters with *γ*-Hydroxyenones, **Keshab Mondal**, and Subhas Chandra Pan, *J. Org. Chem*. **2017**, *82*, 4415.
5. Organocatalytic Asymmetric Dimerization of *γ*-Hydroxyenones to Acetals and Theoretical Investigations into the Diastereoselection, Buddahdeb Mondal, **Keshab Mondal**, Priyadarshi Satpati and Subhas Chandra Pan, *Eur, J. Org. Chem*. **2017**, 7101.
6. Organocatalytic Asymmetric Domino Michael/Acyl Transfer Reaction between *γ/δ*-Hydroxyenones and *α*-Nitroketones, **Keshab Mondal**, and Subhas Chandra Pan, *J. Org. Chem*. **2018**, *83*, 5301.

Presentations

- National Conference on Frontiers in Chemical Sciences (**FICS-2014**), December 4-6, 2014, Indian Institute of Technology Guwahati, India (Poster presentation).
- **ChemConvene 2015**, April 8, Department of Chemistry, IIT Guwahati, India (Poster presentation).
- National Symposium on Natural Products: Prospects & Perspectives (**NPPP-2016**), March 21-22, 2016, CSIR-North East Institute of Science & Technology, Jorhat, Assam, India (Poster presentation).
- **Research Conclave 2016**, IIT Guwahati, India (Poster presentation).

- **ACS on Campus**, January 16, 2017, IIT Guwahati, India (Oral presentation).
- **20th CRSI National Symposium in Chemistry**, February 3-5, 2017, Department of Chemistry, Gauhati University, India (Poster presentation).
- **ChemConvene 2017**, July 25, Department of Chemistry, IIT Guwahati, India (Poster presentation).
- XIII J-NOST Conference for Research Scholars (**J-NOST-2017**), November 9-12, 2017, Department of Chemistry, Institute of Science, Banaras Hindu University (BHU), Varanasi, India (Poster presentation).