DISCOVERY OF DIRECT ORGANOCATALYTIC PUSH-PULL DIENAMINES: SCOPE AND SYNTHETIC APPLICATIONS

A Thesis
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By

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DEDICATED TO

AMMA AND NANNA

DECLARATION

I hereby declare that the entire work embodied in this thesis is the result of investigations carried out by me in the School of Chemistry, University of Hyderabad, Hyderabad, under the guidance of ***Dr. Dhevalapally B. Ramachary*** *and that it has not been submitted elsewhere for any degree or diploma. In keeping with the general practice, due acknowledgements have been made wherever the work described is based on the findings of other investigators.*

RAMAKUMAR KINTHADA

(Candidate)

CERTIFICATE

I hereby certify that the entire work embodied in this thesis has been carried out by Mr. ***Ramakumar Kinthada*** *under my guidance in the School of Chemistry, University of Hyderabad, and that no part of it has been submitted elsewhere for any degree or diploma.*

Dr. DHEVALAPALLY B. RAMACHARY
(THESIS SUPERVISOR)

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UNIVERSITY OF HYDERABAD

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PREFACE

*Nature is the inspiration to develop a new area of catalysis "Organocatalysis" to synthesize stereochemically complex molecules. In this broad area of organocatalysis mainly enamine catalysis, the catalysis of carbonyl transformations via enamine intermediates by using primary and secondary amines as catalysts is fully appreciated as a powerful synthetic tool to design and implementation of new reactions for construction of highly functionalized molecules with good selectivity. The present thesis entitled "**Discovery of Direct Organocatalytic Push-Pull Dienamines: Scope and Synthetic Applications**" describes the reactions involving push-pull dienamine intermediates in cascade reactions and synthesis of highly functionalized molecules. In all sections, a brief introduction is provided to keep the present work in proper perspective, the compounds are sequentially numbered (bold), and references are marked sequentially as superscript and listed at the end of the thesis. All the figures included in the thesis were obtained by DIRECT PHOTOCOPY OF THE ORIGINAL SPECTRA, and in some of them uninformative areas have been cut to save the space.*

Highly functionalized molecules, which are widely used as intermediates in the pharmaceuticals and natural product synthesis. To construct such functionalized molecules a diversity-oriented general, sustainable and practical process for the sequential cascade synthesis is required. Here we discovered direct sequential one-pot combination of amine- or amino acid-catalyzed cascade Knoevenagel/Michael/aldol condensation/decarboxylation with other reactions like amine- or amino acid-catalyzed cascade Claisen-Schmidt/iso-aromatization, Claisen-Schmidt/isomerization, Claisen-Schmidt/iso-aromatization/isomerization, Michael addition, Claisen-Schmidt/Michael reactions of alkyl acetoacetates, variety of aldehydes furnished the highly functionalized push-pull olefins and phenols with high yields. Evidence for a new reaction pathway involving formation of novel push-pull dienamines under amine- or amino acid-catalysis is presented along with examples demonstrating the amenability of the process to multi-catalysis cascade (MCC) chemistry.

Highly functionalized diverse o-hydroxydiarylamine compounds, which are having wide applications and considerable importance in a variety of industries. To construct such complex molecules a diversity-oriented synthesis is required. We reported a practical and

novel one-pot organocatalytic selective process for the cascade synthesis of highly substituted o-hydroxydiarylamines and o-pyrrolidin-1-yldiarylamines. Here we achieved using simple starting materials such as alkyl acetoacetates, aldehydes, and nitrosoarenes furnished the highly functionalized anilines with high yields through direct combination of amine-catalyzed cascade Knoevenagel/Michael/aldol condensation/decarboxylation and cascade enamine amination/isoaromatization. Along with we demonstrated the bio-mimetic auto- and self-catalysis in amine-catalyzed cascade reactions.

In continuation to the organocatalytic cascade reactions based on push-pull dienamine platform highly substituted NH-1,2,3-triazole products and unhydrolyzed 1,2,3-triazoles were synthesized from simple starting materials such as Hagemann's esters and p-toluenesulfonyl azide (TsN_3) in the presence of catalytic amount of L-proline. For the first time through cascade [3+2]-cycloaddition/hydrolysis via a practical and environmentally friendly amino acid catalyzed cascade process was developed for the synthesis of highly substituted NH-1,2,3-triazole products and unhydrolyzed 1,2,3-triazoles. The cascade reaction proceeds in good yields with high selectivity using L-proline as the catalyst. Furthermore, we demonstrated the bio-mimetic solvent induced hydrolysis in amino acid-catalyzed cascade reactions.

In a similar manner, a practical and novel organocatalytic chemo- and enantioselective process for the cascade synthesis of highly substituted 2-alkyl-3-(2-nitro-1-aryl-ethyl)-4-oxo-cyclohex-2-enecarboxylic acid alkyl esters is presented using novel chiral push-pull dienamines. Here we described the synthesis of the L-$(3,5\text{-}Me_2)_2$DPP catalyzed asymmetric Michael reactions of Hagemann's esters with nitroolefins at ambient conditions. This novel asymmetric Michael reaction proceeds in good yields with high selectivity. Along with we demonstrated the synthesis of highly substituted cyclohexenones from chiral Michael adducts using simple decarboxylation as a key step.

LIST OF ABBREVIATIONS

Ac	acetyl
AcOH	acetic acid
Anal.	analysis
aq.	Aqueous
Ar	aryl
Bn	benzyl
Bp	boiling point
br	broad
Bu	butyl
t-Bu or ^{t}Bu	*tertiar*y-butyl
Bz	benzoyl
Calcd.	calculated
cat.	catalytic
cm	centimeter
DABCO	1,4-diazabicyclo(2.2.2)octane
DBU	1,8-diazabicyclo(5.4.0)undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DCM	dichloromethane
DCU	dicyclohexyl urea
dd	doublet of doublet
de	diastereomeric excess
DEPT	distortionless enhancement by polarization transfer
DMAP	dimethylaminopyridine
DME	dimethoxy ethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
DPP	diphenyl prolinol
dr	diastereomeric ratio
dt	doublet of triplet
ee	enantiomeric excess
eq.	equation
equiv.	equivalent(s)
Et	ethyl
EWG	electron withdrawing group
Fig.	figure
gm	gram (s)
h	hour (s)
Hz	hertz
Hex	hexyl
^{i}Pr	isopropyl
IR	infrared
Kcal	kilocalories
LAH	lithium aluminum hydride
lit.	literature
m	multiplet

M	molarity
Mp.	melting point
Me	methyl
mg	milligram (s)
mL	milliliter
mmol	millimole
NMM	*N*-methylmorpholine
NMR	nuclear magnetic resonance
NMP	*N*-methylpyrrolidine
Ph	phenyl
ppm	parts per million
p-TSA	*p*-toluenesulfonic acid
py	pyridine
pr	propyl
q	quartet
RT	room temperature
s	singlet
sec	secondary
t	triplet
TCA	trichloro aceticacid
tert	tertiary
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	toluenesulphonyl
Ms	methanesulphonyl

ABOUT THE AUTHOR

The author, **Mr. Ramakumar Kinthada** was born on 16th August 1982 at Chodavaram, Vishakapatnam Dist, Andhra Pradesh. After his initial schooling in Appalaraju puram, Vishakahapatnam (Dist.) he obtained his B. Sc. degree in 2002 from A. M. A. L. College, Anakapalle; and he obtained his M. Sc. degree in 2004 from University of Hyderabad, Hyderabad. He continued as research scholar in the School of Chemistry, University of Hyderabad for the Ph. D. programme from March 2005 onwards. Presently he is working as a research associate in the department.

LIST OF PUBLICATIONS

1. D. B. Ramachary, **K. Ramakumar** and M. Kishor, Direct organocatalytic in situ generation of novel push–pull dienamines: application in tandem Claisen–Schmidt/iso-aromatization reactions, ***Tetrahedron Lett.*** **2005**, *46*, 7037–7042.
2. D. B. Ramachary, M. Kishor and **K. Ramakumar**, A novel and green protocol for two-carbon homologation: a direct amino acid/K_2CO_3-catalyzed four-component reaction of aldehydes, active methylenes, Hantzsch esters and alkyl halides, ***Tetrahedron Lett.*** **2006**, *47*, 651–656.
3. D. B. Ramachary, **K. Ramakumar** and V. V. Narayana, Organocatalytic cascade reactions based on push-pull dienamine platform: synthesis of highly substituted anilines, ***J. Org. Chem.*** **2007**, *72*, 1458–1463.
4. D. B. Ramachary, V. V. Narayana and **K. Ramakumar,** Direct ionic liquid promoted organocatalyzed diazo-transfer reactions: diversity-oriented synthesis of diazo-compounds, ***Tetrahedron Lett.*** **2008**, *49*, 2704–2709.
5. D. B. Ramachary, V. V. Narayana and **K. Ramakumar,** A new one-pot synthetic approach to the highly functionalized (*Z*)-2-(buta-1,3-dienyl)phenols and 2-methyl-2*H*-chromenes: use of amine, Ruthenium and base-catalysis, ***Eur. J. Org. Chem.*** **2008**, 3907–3911.

6. D. B. Ramachary, **K. Ramakumar** and V. V. Narayana, Amino acid-catalyzed cascade [3+2]-cycloaddition/hydrolysis reactions based on the push–pull dienamine platform: synthesis of highly functionalized *N*H-1,2,3-triazoles, ***Chem. Eur. J.*** **2008**, *14*, 9143–9147.

7. D. B. Ramachary, V. V. Narayana, M. S. Prasad and **K. Ramakumar**, High-yielding synthesis of Nefopam analogues (functionalized benzoxazocines) by sequential one-pot cascade operations, ***Org. Biomol. Chem.*** **2009**, *7*, 3372–3378.

8. D. B. Ramachary, **K. Ramakumar**, A. B. Shashank and V. V. Narayana, Sequential one-pot combination of multi-reactions through multi-catalysis: a general approach to rapid assembly of functionalized push-pull olefins, phenols and 2-methyl-2*H*-chromenes, ***J. Comb. Chem.*** **2010**, *12*, 0000–0000.

9. D. B. Ramachary and **K. Ramakumar**, Direct organocatalytic asymmetric Michael reactions based on the push-pull dienamine platform: synthesis of highly substituted chiral Hagemann's esters (communicated).

POSTERS AND PRESENTATIONS

1. Presented a poster entitled "Amino acid-catalyzed cascade [3+2]-cycloaddition/hydrolysis reactions based on the push–pull dienamine platform: synthesis of highly functionalized *N*H-1,2,3-triazoles" in 6th in-house symposium **"Chemfest-2009"** held at University of Hyderabad, Hyderabad, India on March 7-9, 2009.

2. Given a flash oral presentation entitled "Amino acid-catalyzed cascade [3+2]-cycloaddition/hydrolysis reactions based on the push–pull dienamine platform: synthesis of highly functionalized *N*H-1,2,3-triazoles" in 6th in-house symposium "**Chemfest-2009**" held at University of Hyderabad, Hyderabad, India on March 7-9, 2009.

DISCOVERY OF DIRECT ORGANOCATALYTIC PUSH-PULL DIENAMINES: SCOPE AND SYNTHETIC APPLICATIONS

1. ABSTRACT

A general, sustainable and practical process for the sequential cascade one-pot synthesis of highly substituted push-pull olefins and phenols was reported through multi-catalysis cascade (MCC) reactions. Direct sequential one-pot combination of amine- or amino acid-catalyzed cascade Knoevenagel/Michael/aldol condensation/decarboxylation with other reactions like amine- or amino acid-catalyzed cascade Claisen-Schmidt/iso-aromatization, Claisen-Schmidt/isomerization, Claisen-Schmidt/iso-aromatization/isomerization, Michael addition, Claisen-Schmidt/Michael, reactions of alkyl acetoacetates, variety of aldehydes furnished the highly functionalized push-pull olefins and phenols with high yields. The yields and regioselectivities were good to excellent. Evidence for a new reaction pathway involving formation of novel push-pull dienamines under amine- or amino acid-catalysis is presented along with examples demonstrating the amenability of the process to multi-catalysis cascade (MCC) chemistry.

A practical and novel one-pot organocatalytic selective process for the cascade synthesis of highly substituted *o*-hydroxydiarylamines and *o*-pyrrolidin-1-

yldiarylamines is reported. Direct combination of amine-catalyzed cascade Knoevenagel/Michael/aldol condensation/decarboxylation and cascade enamine amination/isoaromatization of alkyl acetoacetates, aldehydes, and nitrosoarenes furnished the highly functionalized anilines with high yields. Furthermore, we demonstrated the bio-mimetic auto- and self-catalysis in amine-catalyzed cascade reactions.

A practical and environmentally friendly amino acid catalyzed cascade process for the synthesis of highly substituted *N*H-1,2,3-triazole products and unhydrolyzed 1,2,3-triazoles was achieved for the first time through cascade [3+2]-cycloaddition/hydrolysis from simple starting materials Hagemann's esters and *p*-toluenesulfonyl azide (TsN_3) in the presence of catalytic amount of proline. The cascade reaction proceeds in good yields with high selectivity using proline as the catalyst. Furthermore, we demonstrated the bio-mimetic solvent induced hydrolysis in amino acid-catalyzed cascade reactions.

A practical and novel organocatalytic chemo- and enantioselective process for the synthesis of highly substituted 2-alkyl-3-(2-nitro-1-aryl-ethyl)-4-oxo-cyclohex-2-enecarboxylic acid alkyl esters is reported. Here we described the synthesis of L-(3,5-$Me_2)_2$DPP catalyzed asymmetric Michael reactions of Hagemann's esters with nitroolefins at ambient conditions. This novel asymmetric Michael reaction proceeds in good yields with high selectivity using L-(3,5-$Me_2)_2$DPP as a catalyst. Furthermore, we demonstrated the application of chiral Michael products in the synthesis of highly functionalized cyclohexenones.

2. INTRODUCTION

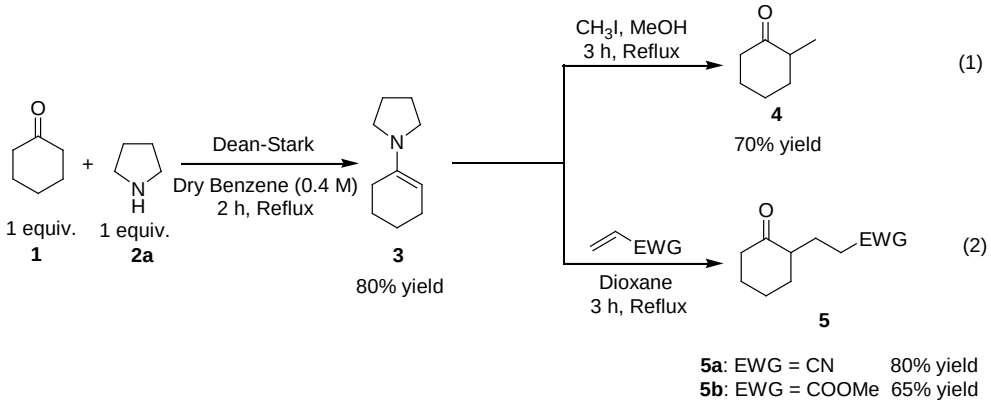
The selective carbon-carbon bond formation is the basic tool for the construction of the molecular frameworks of organic molecules by synthesis. One of the fundamental processes for C–C bond formation is reactions involving enamine intermediates.

Enamines are the intermediates, generated from the reactions of carbonyl compounds with primary or secondary amines as nucleophiles and these enamines have long been recognised as key intermediates in organic synthesis.

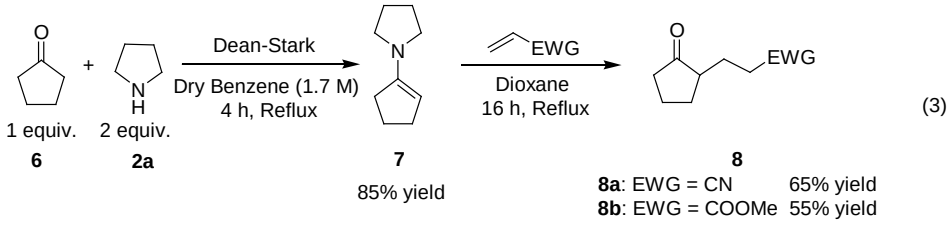
Enamines are genarally used as preformed intermediates for acylation and alkylation of carbonyl compounds. The advantages of enamine reaction over the base-induced alkylation/acylation is no base or other catalyst is required so that it avoids self-condensation reactions of the carbonyl compound and another valuable feature is that it is regioselective. Based on the high regiochemical outcome of the alkylation and acylation reactions from enamine reactions, drives synthetic chemists paying attention to chemistry of enamines. The chemistry of enamines especially their use as nucleophiles in organic synthesis has been investigating since early 1950's.

As the research work described in this thesis deals with reactions involving push-pull dienamines,[1] a brief overview of the reactions involving enamine intermediates are presented below.

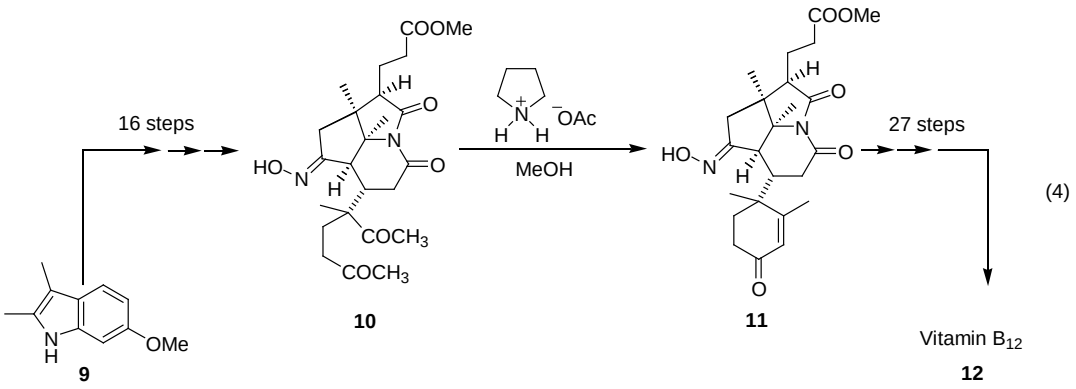
Reactions with enamines was first reported by Strok *et al*. in 1954. In their landmark communication, they have used preformed enamines for the alkylation and acylation of ketones. In this new methodology, pyrrolidine enamine **3** generated from cyclohexanone **1** and pyrrolidine **2a** reacts with methyl iodide in boiling methanol to yield methylated cyclohexanone **4**, and reacts with acrylonitrile and methyl acrylate in boiling dioxane to furnish functionalized cyclohexanones **5** with very good yield as shown in eq. 2.[2]



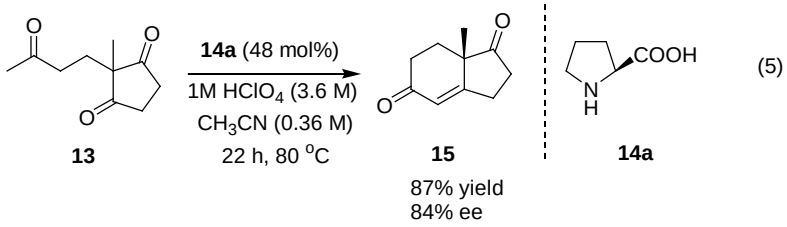
In view of further scrutinizing the enamine reactions, pyrrolidine enamine **7** generated from **6** and **2a**, was treated with acrylonitrile and methyl acrylate in boiling dioxane for 16 hours to furnish functionalized cyclopentanones **8** with good yields as shown in eq. 3. This enamine reaction is an alternative tool for classical base induced acylation and alkylation of carbonyl compounds.



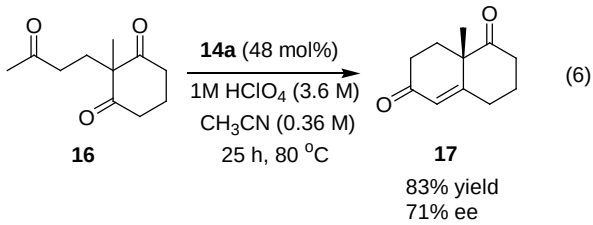
In a continuation of development of chemistry of enamines, Woodward used enamine reaction in a keystep for the synthesis of vitamin-B_{12}. Total synthesis of vitamin-B_{12} is one of the most important and complicated naturally occurring molecule. One among the achievements of Woodward in the field of organic synthesis is the total synthesis of vitamin-B_{12}. In the course of synthesis of vitamin B_{12} functionalized cyclohexenone **11** was synthesized from compound **10** by pyrrolidine acetate in methanol as shown in eq. 4.[3] However here the cyclization is catalyzed by pyrrolidine acetate and in this case the reaction is initiated by enamine formation at the less hindered side of the two carbonyl groups. This clearly shows the Woodward imagination of the potentiality of enamine catalysis.



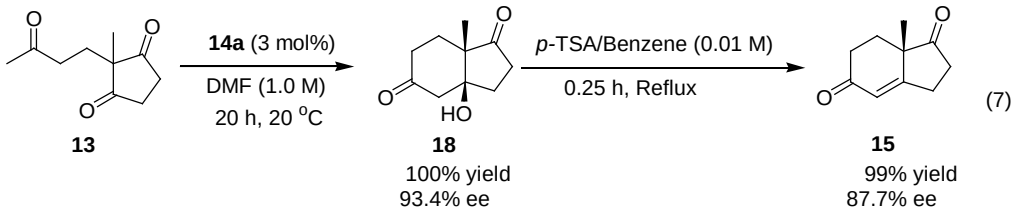
With inspiration from Stork's work, in 1971 Wiechert *et al.* reported the intramolecular asymmetric aldol cyclodehydration of the achiral trione **13** using combination of amino acid and inorganic acid. In this communication they reported synthesis of optically active 7a-methyl-5,6,7,7a-tetrahydro-1,5-indandione **15** which is important starting material for total synthesis of steroids.[4]



This exceptionally elegant approach has also been applied to synthesize optically active Wieland-Miescher ketone **17** with good yield and excellent enantioselectivity as shown in eq. 6.[4] These are very useful building blocks for construction of a broad variety of biologically active compounds such as steroids, terpenoids and taxol.

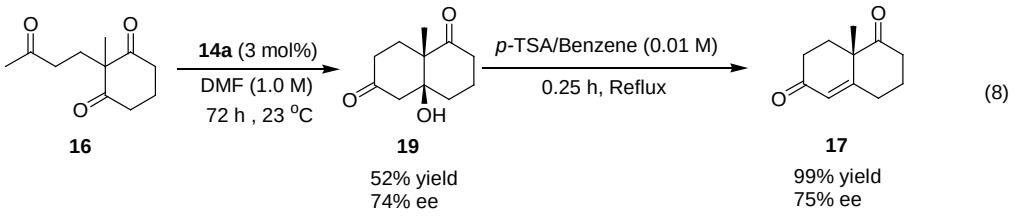


In 1974, Hajos-Parrish discovered the proline catalyzed intramolecular asymmetric aldol cyclodehydration reaction. The investigations by the Hajos group, which included optimization of the reaction conditions, provided detailed insight into the aldol cyclization step and formation of the important intermediate **18**. The best yield and enantioselectivity were obtained when a polar, aprotic solvent was used. In DMF the aldol cyclization of **13** into the ketol intermediate **18** proceeded in quantitative yield and with high enantiomeric excess 93.4% as shown in eq. 7.[5] It is worthy of note that a small amount of L-proline is sufficient for effective catalysis under these conditions and subsequent dehydration of the ketol **18** gave the enone **15** in 99% yield with enantioselectivity 87.7%.



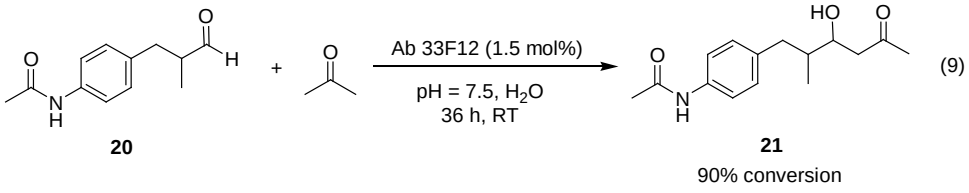
(7)

This approach has also attracted commercial attention because the use of economically attractive catalyst L-proline and also been applied to synthesize optically active Wieland-Miescher ketone **17** which can be used for easy access to the steroid precursors. They revealed that the carboxylic acid functionality and the pyrrolidine ring of proline both were essential for efficient asymmetric induction and this is one of the earliest example for organocatalysis through enamine intermediate. Although this is the first example of an asymmetric intramolecular aldol reaction using an organic molecule, L-proline as chiral catalyst, but neither its mechanism nor its potential for other reactions were realized.



(8)

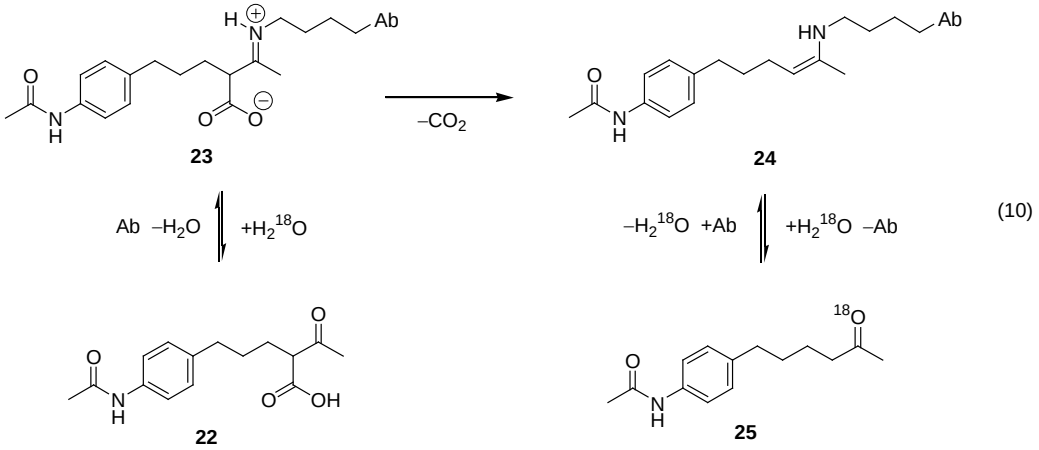
In 1995, Barbas and Lerner co-workers reported the antibodies catalyzed asymmetric aldol reactions. They understand mechanism for this antibody catalysis of the reaction mimics as natural class I aldolase enzymes. Immunization with a reactive compound covalently trapped a lysine residue in the binding pocket of the antibody by formation of a stable enamine. The reaction mechanism for the formation of the covalent antibody-hapten complex was recruited to catalyze the aldol reaction. The antibody 33F12 used the amino group of lysine to form an enamine with acetone and used this enamine as a nascent carbon nucleophile to attack the specially designed aldehyde **20** which gives aldol product **21** by forming a new carbon-carbon bond as shown in eq. 9.[6]



(9)

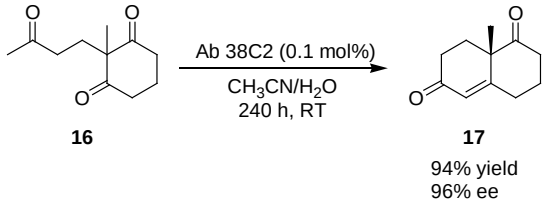
With inspiration from nature's mechanism another report from Barbas group in 1996, is the decarboxylation of *β*-keto acids using catalytic antibodies via enamine intermediates. They have studied antibodies ability to catalyze the decarboxylation of structurally related *β*-keto acids. Both 38C2 and 33F12 aldolase antibodies were shown to efficiently catalyze the decarboxylation. Their studies support the role of an essential lysine residue in the active site of the antibodies and the formation of enamine intermediate in the mechanism. Investigation of the decarboxylation reaction of 2-{3'-(4''-acetamidophenyl)propyl}-acetoacetic acid **22**, to 6-(4'-acetamidophenyl)-2-

hexanone **25**, in the presence of ^{18}O-labeled water by electrospray mass spectrometry revealed incorporation of ^{18}O in the antibody-catalyzed reaction consistent with decarboxylation proceeding via an enamine mechanism as shown in eq. 10.[7]



(10)

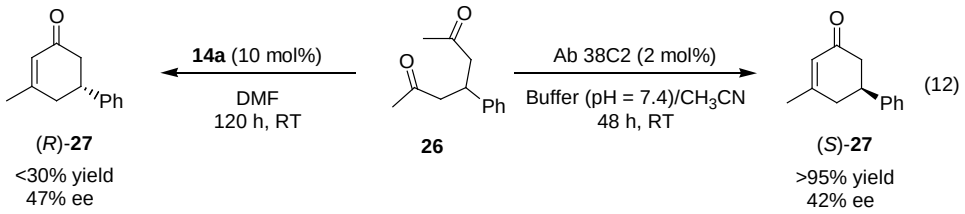
After successful understanding and demonstration of enamine mechanism in antibody catalysis, in 1997 Barbas and Lerner co-workers reported the synthesis of optically active Wieland-Miescher ketone **17** by using biocatalyst (Ab 38C2) as shown in eq. 11.[8] This study drives their interest in organocatalysis, and their comparative studies of aldolase antibodies with L-proline reveals that Hajos-Eder-Sauer-Wiechert reaction proceeds via an enamine reaction mechanism like aldolase antibodies. Mechanistically catalysis with antibody aldolases and the simple amino acid proline are very similar. This study served for launching their studies in organocatalysis.



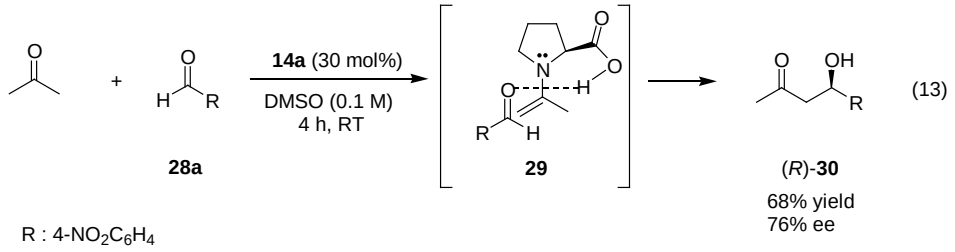
(11)

For further understanding of comparative studies of aldolase antibodies with L-proline, Barbas and Lerner co-workers in 1999, reported that aldolase antibody 38C2 catalyzes the enantioselective aldol cyclodehydration of 4-substituted-2,6-

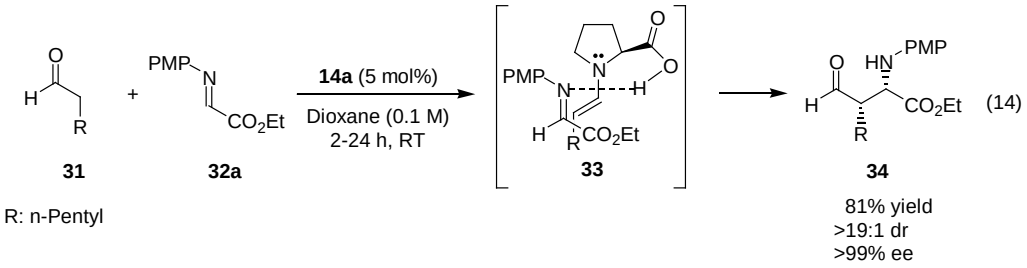
heptanediones **26** to give enantiomerically enriched 5-substituted-3-methyl-2-cyclohexen-1-ones **27** as shown in eq. 12.[9] Enantioselectivities, and product purities are markedly similar to the L-proline catalyzed reactions.



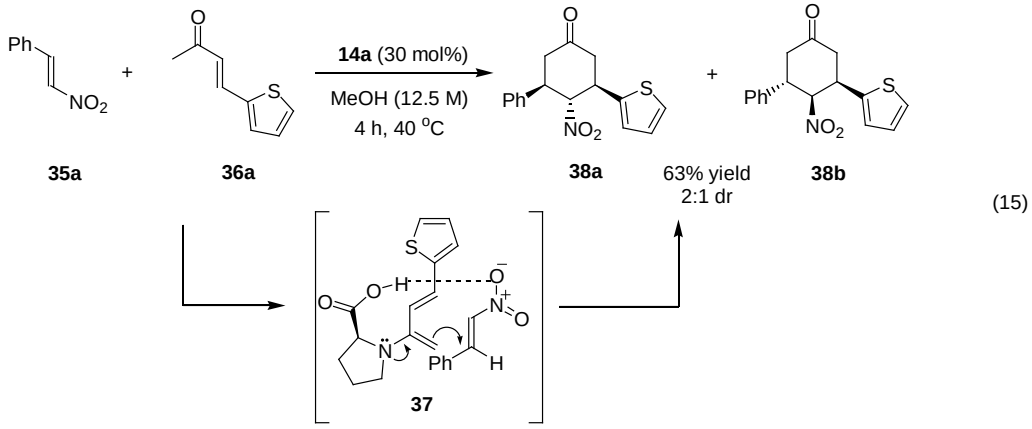
In 2000, Barbas and his co-workers rediscovered the catalytic properties of L-proline by presenting the first enantioselective organocatalytic intermolecular aldol reaction of acetone with 4-nitrobenzaldehyde **28a** at room temperature for 4 hours furnished aldol product (*R*)-**30** in 68% yield and 76% ee with proposed transition state **29** as shown in eq. 13.[10] Following this inspiring report, numerous innovative and increasingly sophisticated examples of the use of aminocatalysis have emerged as an explosive expansion of the field of "organocatalysis" thereby producing a "nearly endless" number of optically active building blocks by applying these ideas.



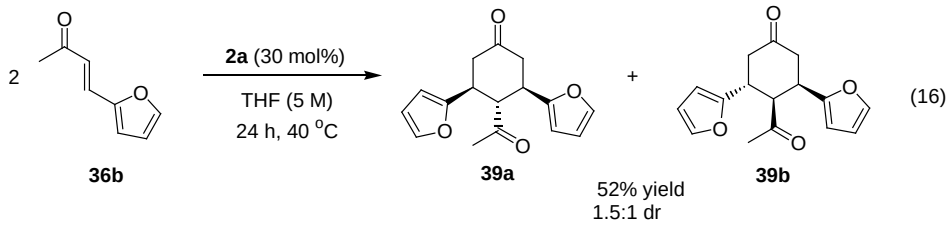
In 2001, Barbas *et al.* described another organocatalytic asymmetric Mannich type reaction. In this report the proline catalyzed reaction of *N*-PMP-protected α-imino ethyl glyoxylate **32a** with heptanal **31** furnished highly enantioselective functionalized protected amino acid **34** with good yield and excellent diastereoselectivity as shown in eq. 14.[11] This is the first report of unmodified aldehydes used as donors in catalytic asymmetric Mannich-type reactions and this reaction is an atom-economic.



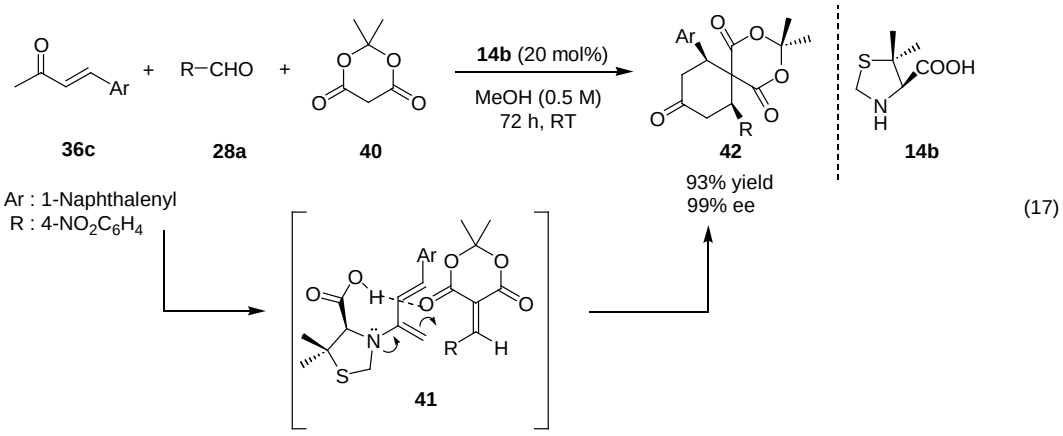
After an initial understanding of enamine catalysis, in 2002 Ramachary and Barbas discovered the reactions involving *in situ* generation of dienamine intermediates named as 2-amino-1,3-diene from α,β-unsaturated ketones and catalytic amount of amines. They demonstrated for the first time amine-catalyzed direct Diels-Alder reactions of α,β-unsaturated ketone **36a** with dienophile **35a** via transition state **37** to provide cyclohexanone derivative **38** as shown in eq. 15.[12] This dienamine catalysis has emerged as a powerful synthetic paradigm and has accelerated the development of new methods involving dienamine intermediates to make diverse chiral molecules.



In the same year Ramachary and Barbas demonstrated, for the first time amine-catalyzed self Diels-Alder (or double Michael) reaction of α,β-unsaturated ketone **36b** providing the synthesis of pro-chiral acyl-substituted cyclohexanone **39** as shown in eq. 16.[13] These new catalytic Diels-Alder reactions afforded an attractive single-step route to functionlized cyclohexanone derivatives.

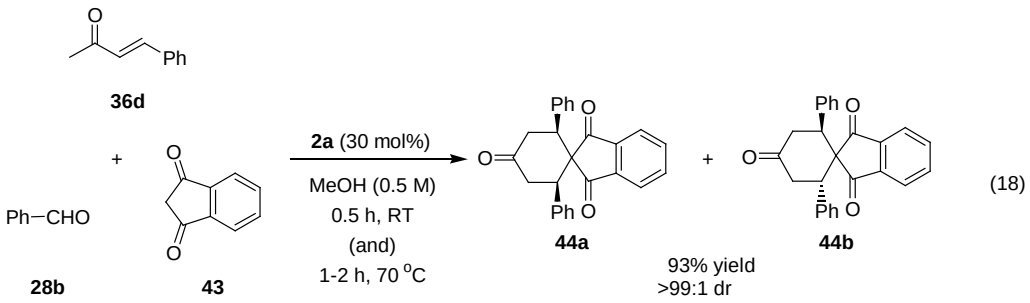


In continuation of their quest in organocatalytic assembly of multicomponent reactions, in 2003 same group reported, the first organocatalytic diastereospecific and enantioselective direct asymmetric domino Knoevenagel/Diels-Alder reaction that produced highly substituted spiro[5,5]undecane-1,5,9-trione **42** via proposed transition state **41** from commercially available 4-substituted-3- buten-2-one **36c**, aldehyde **28a** and 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) **40** as shown in eq. 17.[14] Spirocyclic ketones **42** are attractive intermediates in the synthesis of natural products and in medicinal chemistry, and are the starting materials for the synthesis of exotic amino acids which are used to modify the physical properties and biological activities of peptides, peptidomimetics and proteins.

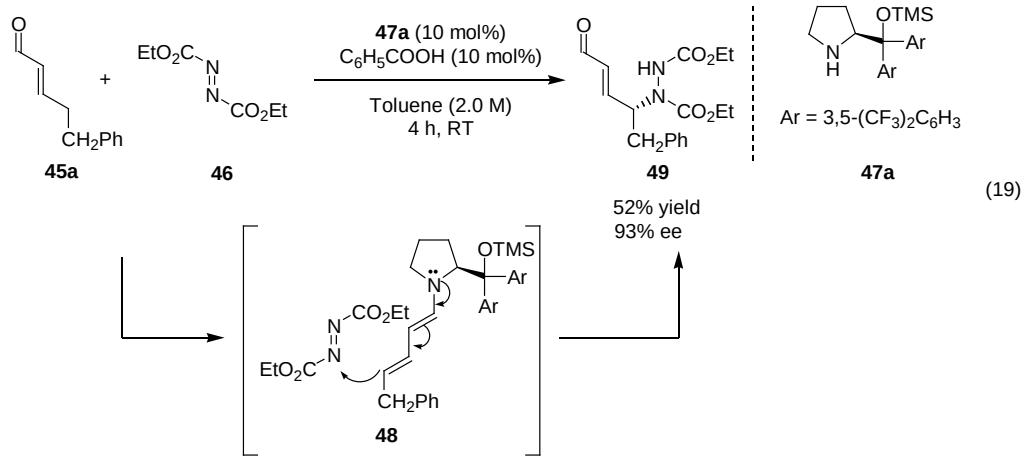


In 2003, Ramachary and Barbas reported the first highly diastereoselective organocatalytic direct hetero-domino Knoevenagel-Diels-Alder-epimerization (K-DA-E) reactions that provide highly substituted prochiral spiro[cyclohexane-1,2'-indan]-1',3',4-trione **44a** from commercially available 4-substituted-3-buten-2-one **36d**, aldehyde **28b** and 1,3-indandione **43** as shown in eq. 18.[15] Spirocyclic ketones **44a** are

the excellent starting materials for the synthesis of fenestranes and for the construction of graphite cuttings bearing a saddle-like, three-dimensionally distorted cores.

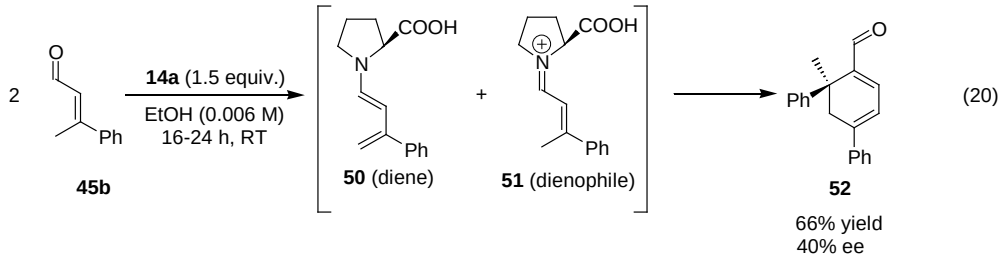


Following these inspiring "dienamine" mediated reports, in 2006 Jørgenson *et al.* reported organocatalytic enantioselective γ-functionalization of α,β-unsaturated aldehyde **45a** with diethyl azodicarboxylate **46** via transition state **48** to provide **49** with moderate yield and high enantioselectivity as shown in eq. 19.[16] They discovered the catalytic amount of secondary amines can invert the usual reactivity of, α,β-unsaturated aldehydes enabling a direct γ-amination of the carbonyl compound using azodicarboxylate as the electrophilic nitrogen-source.

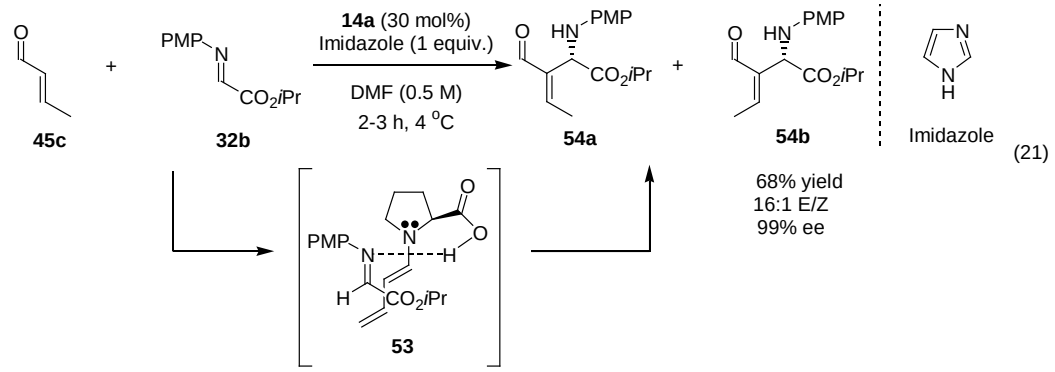


In 2006, Watanabe *et al.* demonstrated the use of proline to promote asymmetric self-condensation of α,β-unsaturated aldehyde **45b** to form trisubstituted cyclohexadiene **52** via diene **50** with good yield and moderate enantioselectivity as shown in eq. 20.[17]

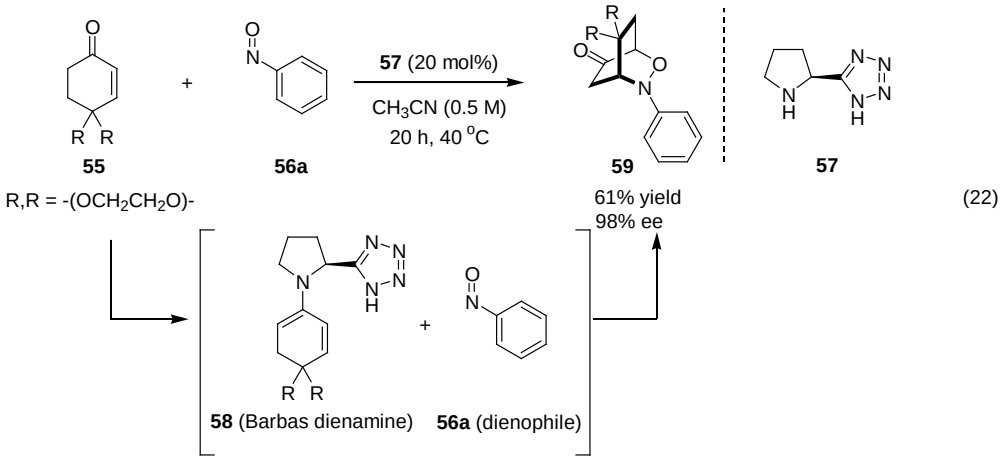
This approach will allow diversification synthesis of these cyclohexadiene ring-fused homodimers in sufficient quantities for biological investigations.



In 2007, Barbas and his co-worker's reported highly enantiomerically enriched aza-Morita-Baylis-Hillman (aza-MBH) type products with β-substituted enal moiety **45c** and *N*-PMP-protected α-imino *iso*-propyl glyoxylate **32b** with transition state **53** to furnish functionalized amino acid **54** with good yield and high enantioselectivity as shown in eq. 21.[18] They reported that this reaction proceeds through dienamine intermediate but not through a typical aza-MBH reaction route.

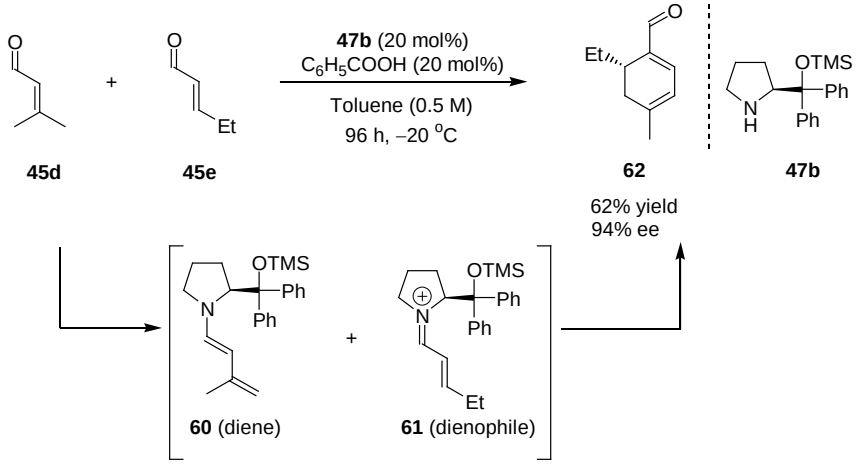


In 2007, Yamamoto *et al.* documented complete regioselective and efficient enantioselective nitroso Diels-Alder reaction by utilizing *in situ*-generated dienamines. The α,β-unsaturated ketone **55** with catalytic amount of **57** *in situ*-generates dienamine which employed as a diene precursor with nitrosobenzene **56a** to provide the cycloadduct **59** in moderate yield with good enantioselectivity as shown in eq. 22.[19]



(22)

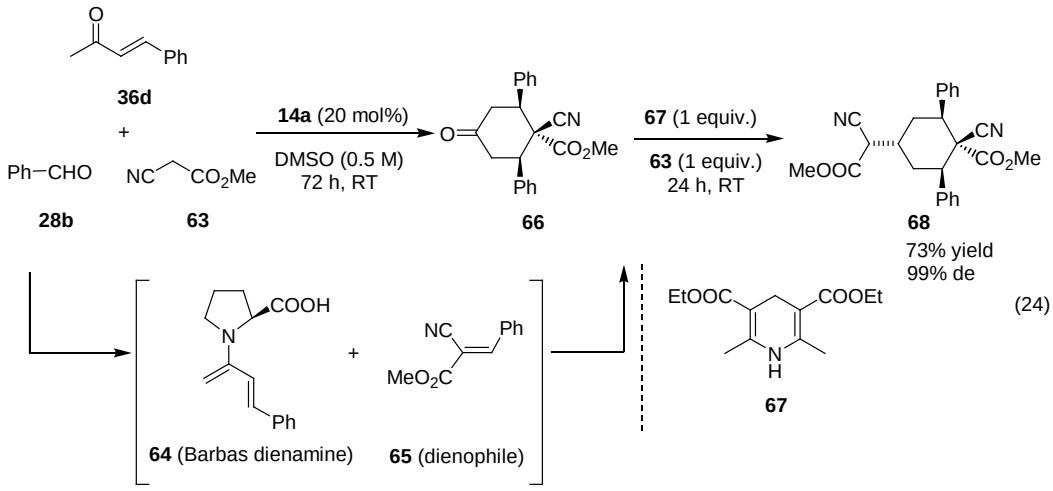
In 2007, Hong *et al.* documented highly enantioselective organocatalytic condensation of α,β-unsaturated aldehydes via formal [4 + 2] cycloaddition. They reported asymmetric condensation of α,β-unsaturated aldehydes **45d** and **45e** to form cyclohexadiene **62** by the formal [4 + 2] cycloaddition through *in situ* generated dienamine **60** as diene. This methodology allows the reaction to proceed at low temperature with moderate yield and higher enantioselectivity as shown in eq. 23.[20]



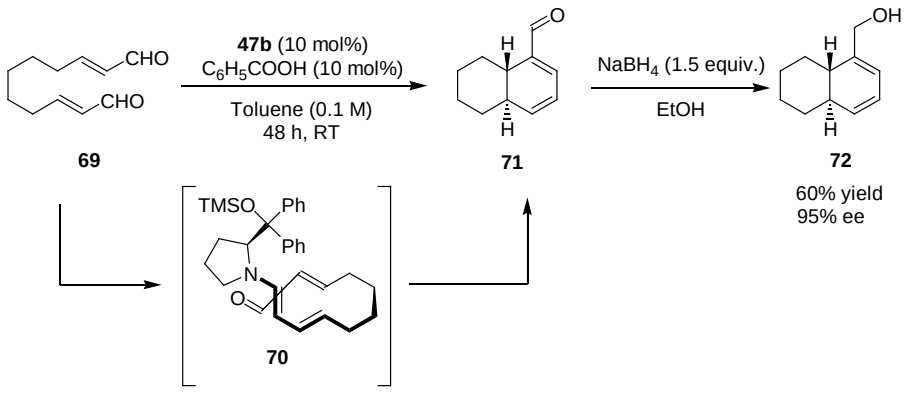
(23)

In 2008, Ramachary *et al.* reported double cascade reactions based on the Barbas dienamine platform for the synthesis of highly stereoselective functionalized cyclohexanes for cardiovascular agents. They reported proline catalyzed three- and five-component cascade olefination-Diels-Alder-epimerization and olefination-Diels-Alder-

epimerization-olefination-hydrogenation reactions of readily available precursor enone **36d**, benzaldehyde **28b**, methyl cyanoacetate **63** and Hantzschester **67** to furnish highly substituted prochiral 1-cyano-4-oxo-2,6-diphenyl-cyclohexanecarboxylic acid methyl ester **66** and 1-cyano-4-(cyano-methoxycarbonyl-methyl)-2,6-diphenyl-cyclohexanecarboxylic acid methyl ester **68** in a highly diastereoselective fashion with excellent yields as shown in eq. 24.[21] Prochiral *cis*-isomers **66** are excellent starting materials for the synthesis of cardiovascular agents and hypnotic active products.

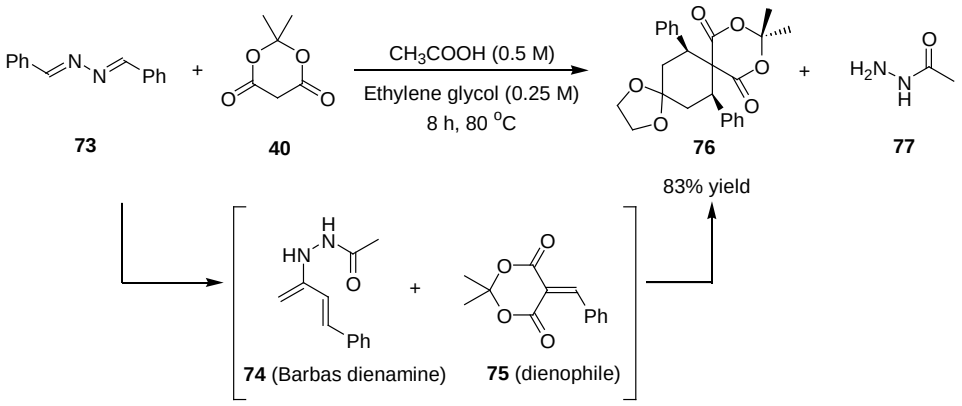


In a similar time, Christmann *et al.* reported the synthesis of novel mono- and bicyclic scaffolds by γ-activation of tethered unsaturated dicarbonyl precursors. Herein, they used diphenylprolinol TMS ether to generate chiral electron-rich dienamine as a diene, which in turn direct the facial approach of α,β-unsaturated carbonyl moiety to furnish cycloadduct **71** which is converted to **72** by simple reduction with good yield and excellent enantioselectivity as shown in eq. 25.[22]



(25)

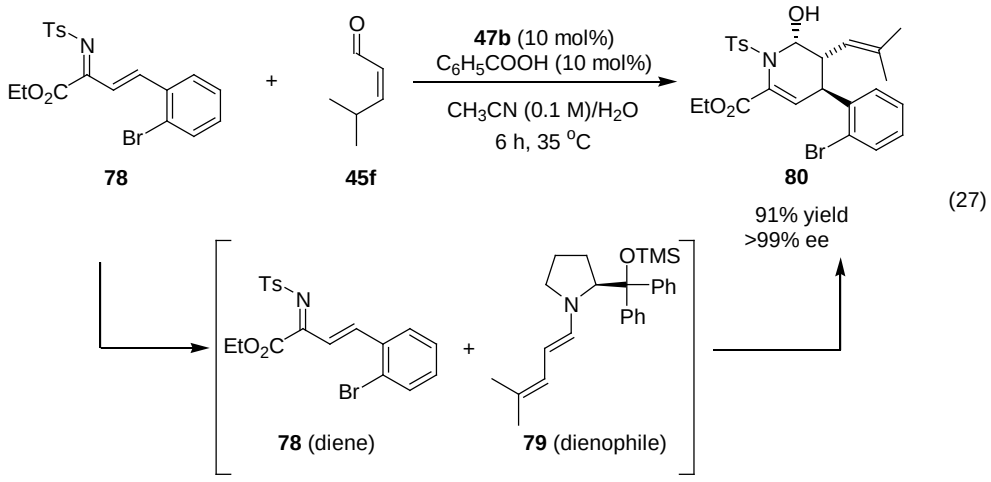
In 2009, Tu *et al.* documented auto-catalysis based on the Barbas dienamine platform, a new domino autocatalytic reaction of imine **73** with Meldrum's acid **40** to furnish polycyclic dispiro[4.2.5.2]pentadecane-9,13-dione **76** derivatives, with remarkable diastereoselectivity in acidic condition. In this reaction byproduct acetohydrazide **77**, plays a critical role in the success of the reaction by serving as a self-catalyst for the Diels-Alder reaction between arylidene-Meldrum's acid **75** and Barbas dienamine **74** as shown in eq. 26.[23]



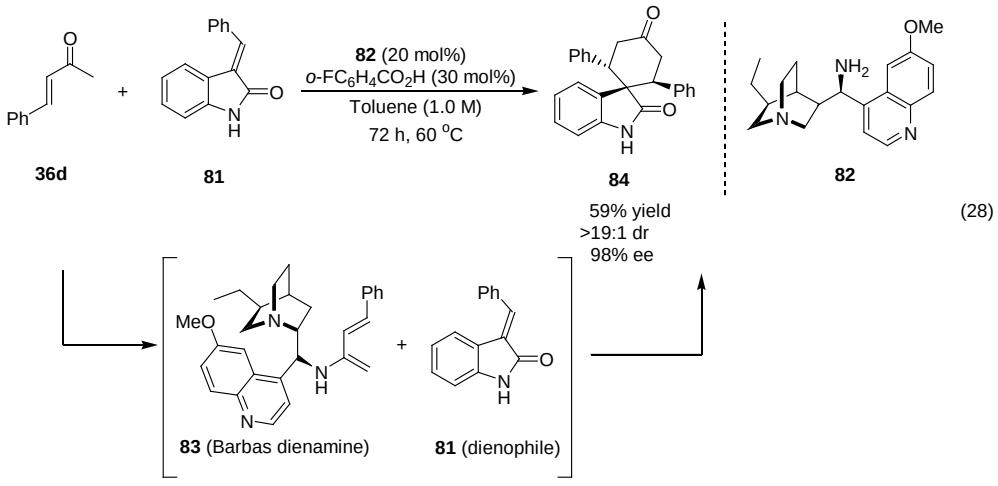
(26)

In a similar time, Chen *et al.* reported the highly regio- and stereoselective synthesis of functionalized chiral hemiaminal **80** with 91% yield and >99% enantiomeric excess from *N*-tosyl-1-aza-1,3-butadiene **78** as a diene and *in situ* generated dienamine **79** as a dienophile via inverse-electron-demand aza-Diels-Alder reaction as shown in eq. 27.[24] The resulting densely functionalized enantiomerically

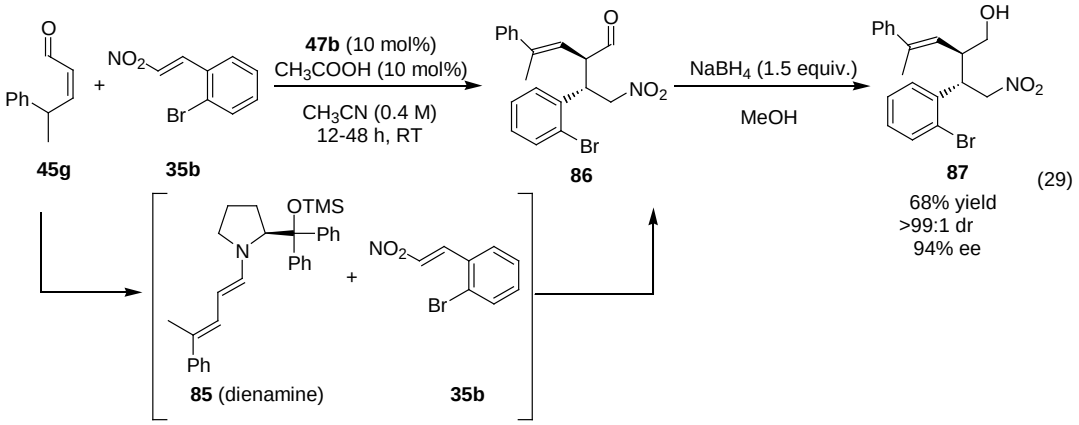
pure hemiaminal derivative **80** is useful in the total synthesis of natural products and medicinal chemistry.



In 2009, Melchiorre *et al.* reported synthesis of spirocyclic oxindoles having multiple stereocenters through Barbas dienamine Platform. In this report, Barbas dienamine intermediate **83** which is *in situ* generated from α,β-unsaturated ketone **36d** reacts with dienophile **81** to afford the spiro-oxindole derivative **84** with good yield and moderate diastereoselectivity with high enantioselectivity as shown in eq. 28.[25] This spirocyclic oxindole core is found in a number of natural products and as well as medicinally relevant compounds.



In a similar time, Chen *et al.* reported that first direct chemo and regioselective Michael addition of γ,γ-disubstituted α,β-unsaturated aldehydes to nitroolefins via dienamine catalysis. The α,β-unsaturated aldehyde **45g** *in-situ* generates dienamine **85** which on treatment with nitroolefin **35b** furnished Michael adduct **86** which is converted to **87** by simple reduction with good yield and excellent enantioselectivity as shown in eq. 29.[26] These products have synthetic significance in medicinal chemistry.



In continuation of synthesis of highly functionalized molecules starting from the simple materials in one-pot,[27] research work has been carried out on the synthesis of functionalized molecules in a single step, and the results are presented in this thesis.

To begin with, starting from simple starting materials, reactions involving push-pull dienamines were developed[1] for the one-pot synthesis of functionalized molecules and the results are presented in the next sections.

3. SEQUENTIAL ONE-POT COMBINATION OF MULTI-REACTIONS THROUGH MULTI-CATALYSIS: A GENERAL APPROACH TO RAPID ASSEMBLY OF FUNCTIONALIZED PUSH-PULL OLEFINS AND PHENOLS

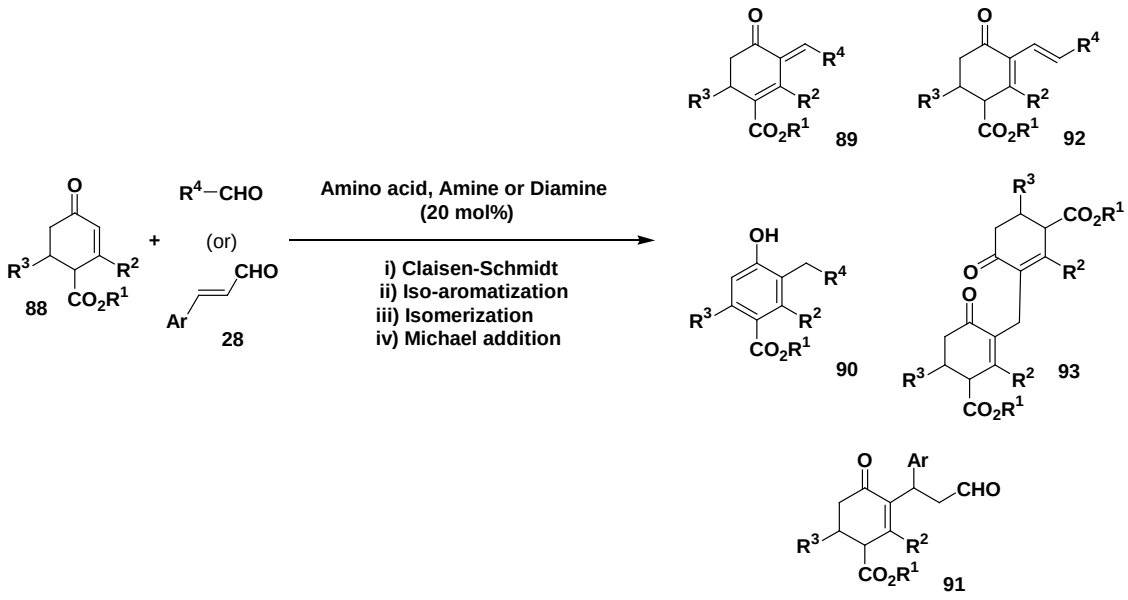
3.1 INTRODUCTION

Critical objectives in modern synthetic organic chemistry include the catalytic asymmetric assembly of simple and readily available precursor molecules into stereochemically and electronically complex compounds under sustainable reaction conditions as mimicking cellular reactions. In this regard, the development of one-pot sequential combination of multi-catalysis and multi-component reaction methodologies can provide expedient access to complex products from simple starting materials.[28] Recently, amine- or amino acid-catalysis (organocatalysis) has emerged as a promising sustainable synthetic tool for the constructing combination of C-C, C-N, C-O, C-S, C-P, C-F and/or C-H bonds in a single operation with high diastereo- and enantioselectivity in a cascade or multi-component process.[29] Generally in organocatalysis, structurally simple and stable chiral organoamines and amino acids facilitate iminium- and enamine-based transformations with carbonyl compounds and are used as catalysts in operationally simple and environmentally friendly cascade reactions.

As part of our research program to engineer direct combination of organocatalytic multi-component and multi-catalysis reactions,[27d-l] herein we report the organocatalytic regioselective direct cascade Claisen-Schmidt/iso-aromatization (CS/IA), Claisen-Schmidt/isomerization (CS/I), Claisen-Schmidt/iso-aromatization/isomerization (CS/IA/I), Claisen-Schmidt/Michael (CS/M) and Michael addition that produce highly substituted 2-arylidene or 2-alkylidene cyclohexanones

(push-pull olefins) **89**, highly substituted push-pull phenols **90**, functionalized aldehydes **91**, highly functionalized (*E*)-1,3-dienes **92**, functionalized bis-enones **93** from commercially available Hagemann's esters **88**, aldehydes **28** and amines or amino acids **2** or **14** as shown in Scheme 1. Push-pull olefins and phenols **89**/**90** are attractive intermediates in the synthesis of natural products and in medicinal chemistry[30] also in organic synthesis (see Chart 1). Hence, their economical and environmental friendly preparation has continued to attract considerable synthetic interest in developing new methods for their synthesis.[31]

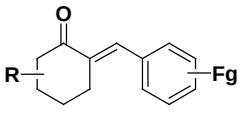
Scheme 1: Direct Organocatalytic Sequential One-pot Cascade Reactions Based on the Push-Pull Dienamine Platform



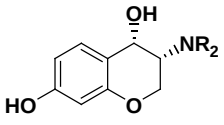
We envisioned that an amine- or amino acid would catalyze the cascade Claisen-Schmidt condensation of variety of aldehydes **28** with *in situ* generated push-pull dienamine (1-amino-1,3-butadiene)[1] intermediate from Hagemann's esters **88** and amine/amino acid **2**/**14** to form substituted push-pull olefins (3-arylidene Hagemann's ester) **89** in a highly regioselective manner, which then undergoes iso-aromatization to produce substituted push-pull phenols **90**, isomerization to produce substituted (*E*)-1,3-

dienes **92** or Michael addition with **88** to produce substituted bis-enones **93** under base-catalysis based on the electronic nature of aldehydes **28**.

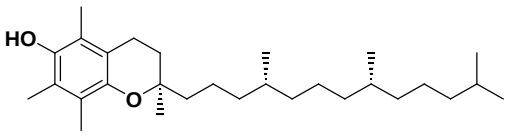
Chart 1: Some Natural/Non-natural Products and Pharmaceuticals Containing Cascade Compounds Obtained from Push-Pull Dienamine Chemistry



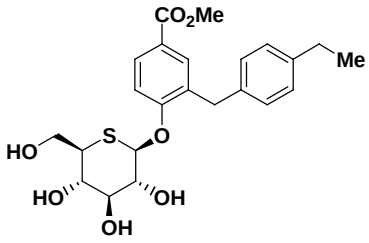
A
Anti-cancer/Anti-inflammatory



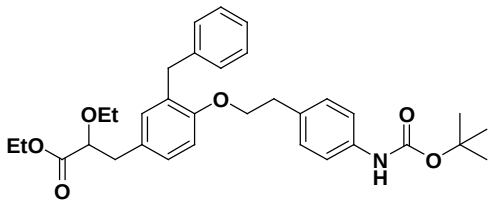
B
NMDA Antagonists



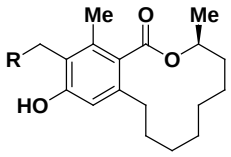
C
Vitamin E



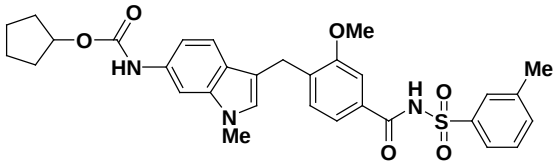
D
Remedies for Diabetes



E
Insulin Resistance



G
Lasiodiplodin Analogues



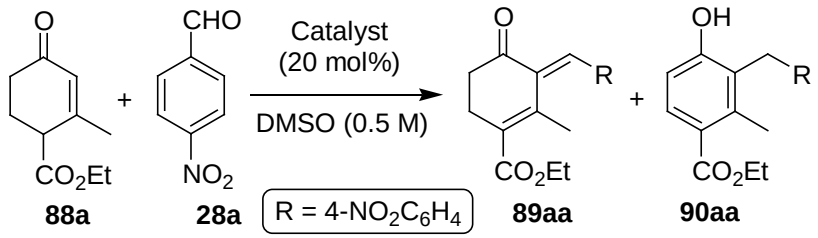
F
Antiasthmatic LTD4 Antagonist
ICI-204,219

3.2 RESULTS AND DISCUSSION

3.2.1 Direct Amino acid-Catalyzed Claisen-Schmidt Condensation: Reaction Optimization: We were surprised to find that the reaction of Hagemann's ester **88a** and 4-nitrobenzaldehyde **28a** with a catalytic amount of L-proline **14a** in DMSO at 25 °C or 75 °C for 48 h or 24 h respectively, didn't furnished the expected

products **89aa** or **90aa** as shown in Table 1, entries 1 and 2. Interestingly, the same reaction catalyzed by phenylalanine **14c** at 25 °C for 96 h furnished the Claisen-Schmidt (CS) product **89aa** as a 1.25:1 mixture of *E*/*Z* isomers in 40% yield and without formation of cascade product **90aa** (Table 1, entry 3).

Table 1: Optimization of the Direct Amino acid Catalyzed Cascade Claisen-Schmidt and Iso-aromatization reaction of **88a** and **28a**[a]



88a **28a** **89aa** **90aa**

entry	catalyst	temp (°C)	time (h)	yield (%)[b] **89aa**	yield (%)[b] **90aa**
1[c]	proline **14a**	25	48	–	–
2[c]	proline **14a**	75	24	–	–
3[d]	phenylalanine **14c**	25	96	40	–
4[d]	**glycine 14d**	**25**	**24**	**73**	**–**
5[d,e]	glycine **14d**	25	96	55	–
6[e]	pyrrolidine **2a**/AcOH	25	12	–	30

[a] Reactions were carried out in DMSO (0.5 M) with the same proportions of Hagemann's ester **88a** and aldehyde **28a** in the presence of 20 mol% catalyst. [b] Yield refers to the column-purified product. [c] 70 to 85% of unreacted Hagemann's ester **88a** was isolated. [d] 1.25:1 Mixture of *E*/*Z* isomers were isolated. [e] DMF was used as the solvent.

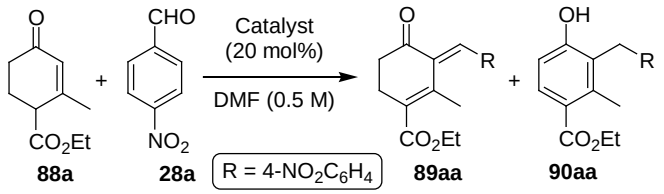
In a similar manner, reaction of **88a** with **28a** under glycine **14d**-catalysis in DMSO at 25 °C for 24 h furnished the CS product **89aa** as a 1.25:1 mixture of *E*/*Z* isomers in 73% yield and without cascade product **90aa** (Table 1, entry 4). But unfortunately, same

reaction took longer reaction time with lesser yield in DMF as solvent (Table 1, entry 5). Interestingly, the cascade reaction catalyzed by bifunctional catalyst, pyrrolidine **2a**/AcOH at 25 °C for 12 h furnished the Claisen-Schmidt/iso-aromatization (CS/IA) product **90aa** in 30% yield and without isolation of CS product **89aa** as shown in Table 1, entry 6. The optimal reaction conditions for push-pull olefin synthesis involved glycine **14d**-catalysis at 25 °C in DMSO with equimolar quantities of **88a** and **28a**, which furnished the CS product **89aa** in 73% yield (Table 1, entry 4). The regiochemistry of products **89aa** and **90aa** was established by NMR analysis.

3.2.2 Direct Amine-Catalyzed Cascade Claisen-Schmidt/Iso-aromatization

Reaction Optimization: Based on the result of Table 1, entry 6, we screened several pyrrolidine-based catalysts **2** by monitoring the reaction yield and regioselectivity of the cascade reaction of **88a** and **28a** in DMF (Table 2). In the cascade Claisen-Schmidt/iso-aromatization (CS/IA) reaction of ester **88a** and 4-nitrobenzaldehyde **28a** catalyzed directly by amine **2a**, we found that the solvent had a significant effect on the rates and yields (Table 2). The results of this investigation indicated that the cascade CS/IA reaction catalyzed by amine **2a** produced the product **90aa** with good yields in aprotic dipolar solvents like DMF and DMSO (Table 2, entries 1–13) but did not furnish products **89aa** and **90aa** in protic polar solvents (H_2O, MeOH, EtOH, $CHCl_3$, CH_3CN, CH_2Cl_2), the aprotic polar solvent (THF) and in the ionic liquid [bmim]BF_4 (results not presented in Table 2). The amine-induced Claisen-Schmidt condensation is strongly solvent-dependent reaction. The first step, the formation of the 1-amino-1,3-butadiene from the keto ester **88a** and amine, and its addition to the carbonyl (or imine) group is facilitated in solvents of high polarity and the second step, 1,2-elimination, is inhibited by protic solvents. Thus, dipolar aprotic solvents such as DMF and DMSO are especially useful for amine-catalyzed Claisen-Schmidt condensations.[1]

Table 2: Optimization of the Direct Amine Catalyzed Cascade Claisen-Schmidt and Iso-aromatization reaction of **88a** and **28a**[a]



entry	catalyst	temp (°C)	time (h)	yield (%)[b] **89aa**	yield (%)[b] **90aa**
1	pyrrolidine **2a**	25	6	–	65
2	**pyrrolidine 2a**	**25**	**12**	**–**	**75**
3[c]	**pyrrolidine 2a**	**25**	**12**	**–**	**77**
4[d]	pyrrolidine **2a**	25	2	60	5
5	pyrrolidine **2a**	60	2	–	61
6[e]	pyrrolidine **2a**	25	23	–	65
7	piperidine **2b**	25	12	–	61
8[f]	morpholine **2c**	25	12	–	–
9	benzylamine **2d**	25	24	30	–
10[f]	aniline **2e**	25	24	–	–
11[f]	DMAP **2f**	25	96	–	–
12[f]	triethylamine **2g**	25	12	–	–
13[f]	DBU **2h**	25	12	–	–

[a] Reactions were carried out in DMF (0.5 M) with the same proportions of Hagemann's ester **88a** and aldehyde **28a** in the presence of 20 mol% catalyst. [b] Yield refers to the column-purified product. [c] 1.25 equivalents of ester **88a** was used. [d] 1:1 mixture of *E*/*Z* isomers were isolated. [e] DMSO was used as the solvent. [f] 70 to 85% of unreacted Hagemann's ester **88a** was isolated.

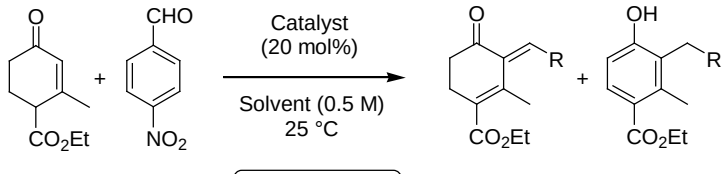
The structurally simple pyrrolidine **2a** catalyzed the cascade CS/IA reaction of **88a** and **28a** to produce **90aa** in 65% yield at 25 °C for 6 h and extension of the reaction time to 12 h furnished the **90aa** in 75% yield (Table 2, entries 1 and 2). Interestingly, the same reaction performed at 25 °C for 2 h furnished the **89aa** in 60% yield with 1:1 mixture of *E/Z* isomers and **90aa** in 5% yield (Table 2, entry 4). At 60 °C, the same

reaction with pyrrolidine **2a** furnished the cascade CS/IA product **90aa** in 61% yield in reduced time (Table 2, entry 5). As discussed in above, cascade CS/IA reaction of **88a** and **28a** under **2a**-catalysis in DMSO at 25 °C for 23 h furnished the product **90aa** in only 65% yield as shown in Table 2, entry 6. Piperidine **2b** also catalyzed the cascade CS/IA reaction in 61% yield, but there is no reaction under morpholine **2c**-catalysis (Table 2, entries 7 and 8). Primary amines like benzylamine **2d** catalyzed the CS reaction of **88a** and **28a** to furnish **89aa** in 30% yield, but there is no reaction under aniline **2e**-catalysis (Table 2, entries 9 and 10). The *tert*-amines like DMAP **2f**, triethylamine **2g** and DBU **2h** did not catalyzed the cascade CS or CS/IA reaction, which is strong evidence for the intermediate enamine formation during these reactions. The optimal reaction conditions for push-pull phenol synthesis involved pyrrolidine **2a** catalysis at 25 °C in DMF with equimolar quantities of **88a** and **28a**, which furnished the cascade CS/IA product **90aa** in 75% yield (Table 2, entry 2).

3.2.3 Direct Diamine-Catalyzed Cascade Claisen-Schmidt/Iso-aromatization Reaction Optimization: After successful demonstration of glycine- and pyrrolidine-catalyzed cascade CS and CS/IA reactions, we further screened diamine-based catalysts to increase the reaction yield and regioselectivity of the cascade reaction of **88a** and **28a** (Table 3). The structurally simple diamine, (*S*)-1-(2-pyrrolidinyl-methyl)pyrrolidine **2i** catalyzed the cascade CS/IA reaction of **88a** and **28a** at 25 °C for 7 h in DMF to produce **90aa** in 75% yield (Table 3, entry 1). Interestingly, the same reaction in DMSO at 25 °C for 7 h furnished the cascade CS/IA product **90aa** in 80% yield and which is better-optimized condition compared to glycine- and pyrrolidine-catalysis (Table 3, entry 2). Surprisingly, cascade CS/IA reaction of **88a** and **28a** under (*S*)-1-pyrrolidin-2-ylmethyl-piperidine **2j**-catalysis in DMF or DMSO at 25 °C for 8 h furnished the product **90aa** in 62-66% yield, which is not superior compared to **2i**-catalysis (Table 3, entries 3 and 4). The optimized conditions for the CS/IA reaction of **88a** and **28a** in DMSO at 25 °C for 7 h to furnish **90aa** with excellent

conversions and yields required the presence of the catalytic amount of (*S*)-1-(2-pyrrolidinyl-methyl)pyrrolidine **2i** (Table 3, entry 2).

Table 3: Optimization of the Direct Diamine-Catalyzed Cascade Claisen-Schmidt and Iso-aromatization reaction of **88a** and **28a**[a]



88a **28a** R = 4-$NO_2C_6H_4$ **89aa** **90aa**

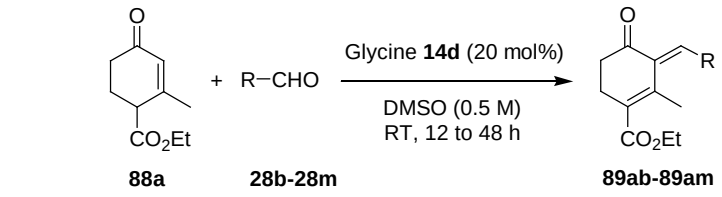
2i **2j**

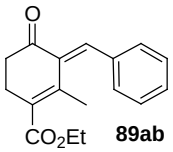
entry	catalyst	solvent (0.5 M)	time (h)	yield (%)[b] **89aa**	yield (%)[b] **90aa**
1	diamine **2i**	DMF	7	–	75
2	**diamine 2i**	**DMSO**	**7**	**–**	**80**
3	diamine **2j**	DMF	8	–	62
4	diamine **2j**	DMSO	8	–	66

[a] Reactions were carried out in DMF or DMSO (0.5 M) with the same proportions of Hagemann's ester **88a** and aldehyde **28a** in the presence of 20 mol% catalyst. [b] Yield refers to the column-purified product.

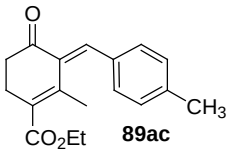
3.2.4 Diversity-Oriented Synthesis of Push-Pull Olefins 89ab-am via Glycine-Catalysis: With an efficient amino acid-catalyzed CS protocol in hand, the scope of the glycine-catalyzed CS reactions was investigated with various aldehydes **28b-m**. A series of neutral, electron-donating, electron-withdrawing and α,β-unsaturated aldehydes **28b-m** were reacted with 1.0 equiv. of Hagemann's ester **88a** catalyzed by 20-mol% of glycine **14d** at 25 °C for 12-48 h in DMSO (Table 4). Interestingly, in all these reactions iso-aromatization did not taken place and only the CS products, 3-arylidene Hagemann's esters **89ab-89am** were isolated in moderate to

Table 4: Synthesis of Chemically Diverse Libraries of 3-Arylidene-Hagemann's Esters **89** via Glycine-Catalysis[a]

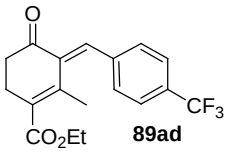




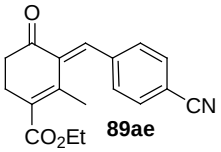
Yield:[b] 80%
Ratio *E*/*Z*[c] = 3.5:1



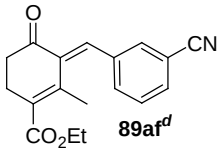
Yield: 70%
E/*Z* = 3.5:1



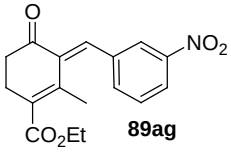
Yield: 81%
E/*Z* = 2.0:1



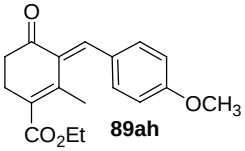
Yield: 71%
E/*Z* = 2:1



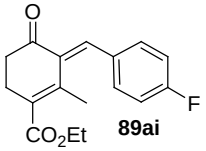
Yield: 55%
E/*Z* = 10:1



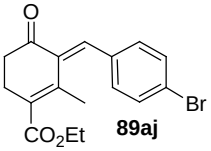
Yield: 55%
E/*Z* = 1.5:1



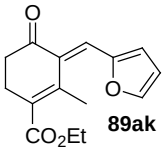
Yield: 55%
E/*Z* = 3.3:1



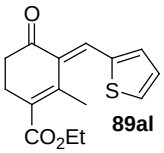
Yield: 70%
E/*Z* = 5:1



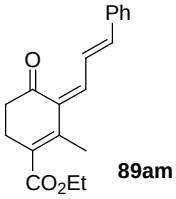
Yield: 62%
E/*Z* = 3:1



Yield: 81%
E/*Z* = 6:1



Yield: 60%
E/*Z* = 2:1



Yield: 50%
E/*Z* = 1:8

[a] All reactions were carried out in DMSO (0.5 M) with the same proportions of Hagemann's ester **88a** and aldehyde **28** in the presence of 20 mol% glycine. [b] Yield refers to the column-purified product. [c] *E*/*Z* ratio determined by NMR analysis. [d] Hagemann's ester **88a** (1.0 mmol) reacted with aldehyde **28f** (0.5 mmol) in the presence of 20 mol% glycine **14d** at 65 ^{o}C for 12 h.

good yields and with stereoselectivities favouring the *E*-isomers except in the case of α,β-unsaturated aldehyde **28m**.

The ethyl (*E*)-3-benzylidene-2-methyl-4-oxo-cyclohex-1-enecarboxylate **89ab** and ethyl (*E*)-2-methyl-3-(4-methyl-benzylidene)-4-oxo-cyclohex-1-enecarboxylate **89ac** were obtained as major isomers with excellent yields via **14d**-catalyzed CS reaction of **88a** with **28b**/**28c** respectively (Table 4). Interestingly, the CS reaction of **88a** with 4-trifluoromethyl-benzaldehyde **28d** under glycine **14d**-catalysis furnished the ethyl (*E*)-2-methyl-4-oxo-3-(4-trifluoromethyl-benzylidene)-cyclohex-1-enecarboxylate **89ad** as major isomer in 81% yield (Table 4). The CS reaction of **88a** with benzaldehydes **28e-g** containing electron-withdrawing groups also under glycine **14d**-catalysis furnished the CS products (*E*)-**89ae-ag** as major isomers with 10:1 to 1.5:1 dr ratio with good yields (Table 4). Interestingly, halogenated benzaldehydes **28i-j** and heterocyclic aldehydes **28k-l** also furnished the expected CS products **89ai-al** with **88a** under **14d**-catalysis in good yields with *E*-isomer as major (Table 4). Structure and regiochemistry of CS products **89ab-al** were confirmed by ^{1}H NMR, ^{13}C NMR [for example see Fig. 1] and mass analysis. Reaction of **88a** with *trans*-cinnamaldehyde **28m** under glycine **14d** catalysis furnished the CS product **89am** in 50% yield with a 1:8 *E/Z* ratio. The regiochemistry of **89am** was established based on a deuterium labeling experiment, nOe experiments and MMX calculations.[1a] The results in Table 4 demonstrate the broad scope of this novel CS methodology covering a structurally diverse group of aldehydes **28b-m** with good yields and selectivity. 2-Arylidenecyclohexanones, 2,6-bis(arylidene)-cyclohexanones and related compounds were evaluated for anti-tumor, anti-inflammatory, anti-neoplastic, cytotoxic activity and also for the inhibition of mitochondrial function in yeast emphasizing the value of this amino-acid catalyzed CS approach.[30a-e] In addition, generation of molecular diversity around the 2-arylidenecyclohexanone scaffolds may allow for the identification of more potent species.

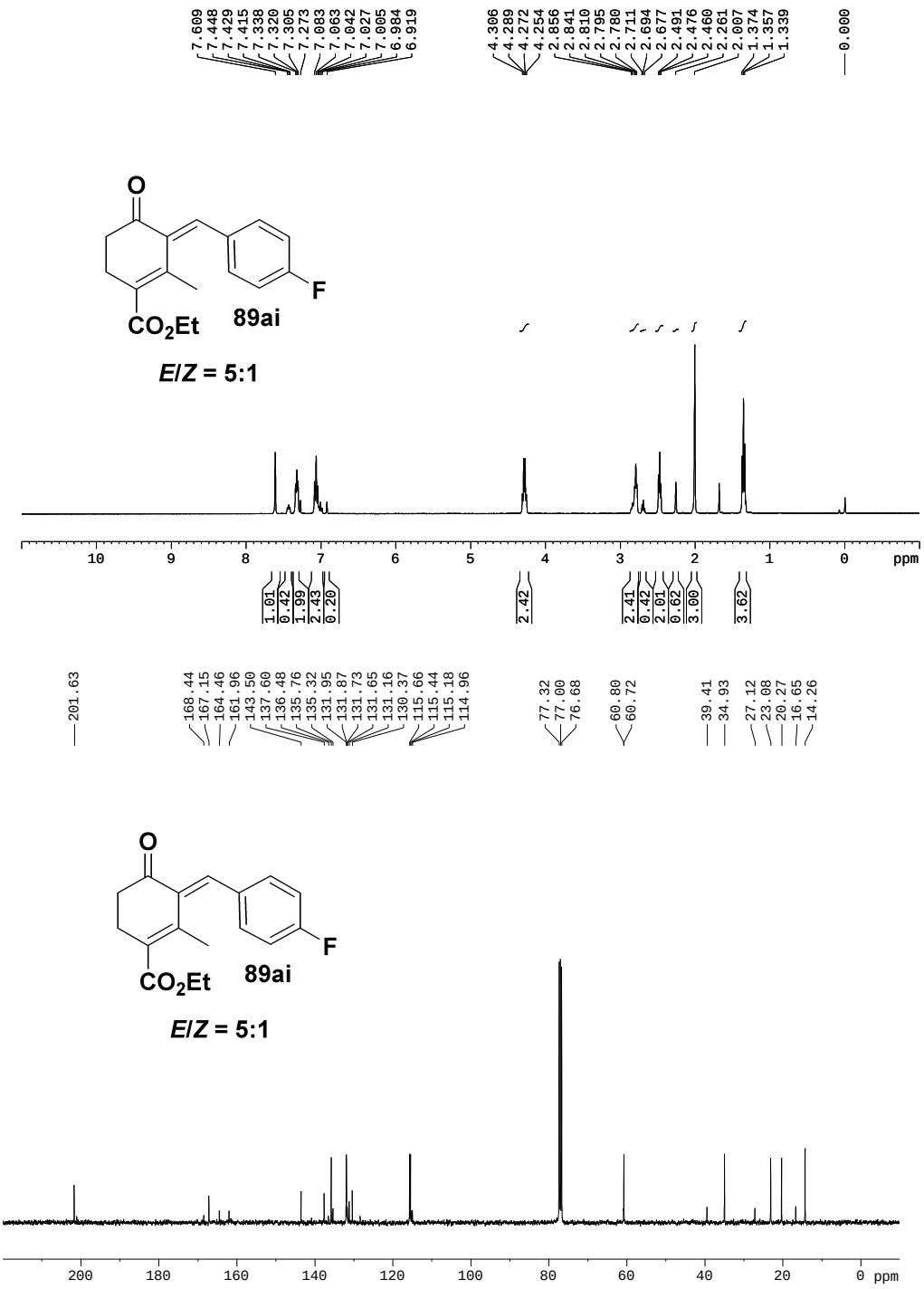
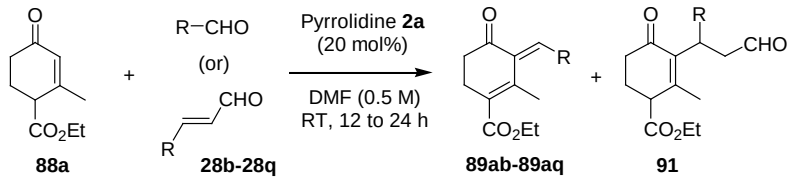


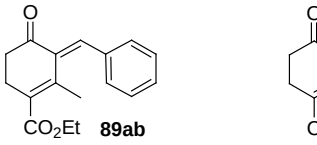
Figure-1: ^{1}H NMR and ^{13}C NMR Spectrum of product **89ai**.

3.2.5 Diversity-Oriented Synthesis of Push-Pull Olefins 89ab-89ap and Functionalized Aldehydes 91am/91aq via Pyrrolidine-Catalysis: After successful demonstration of glycine **14d**-catalyzed CS reactions with various aldehydes **28b-m**, we further showed interest to screen similar reactions under pyrrolidine **2a**-catalysis to test the iso-aromatization of *in situ* generated CS products **89ab-am** by monitoring to the electronic nature of aldehydes **28** or/and basic nature of catalyst **2a** in cascade CS/IA reactions (Table 5). As shown in Table 5, a series of neutral, electron-donating, electron-withdrawing and α,β-unsaturated aldehydes **28b-q** were reacted with 1.0 equiv. of Hagemann's ester **88a** catalyzed by 20 mol% of pyrrolidine **2a** at 25 °C for 12-24 h in DMF. But unfortunately, in these reactions also iso-aromatization did not taken place and only the CS products, 3-arylidene Hagemann's esters **89ab-ap** and Michael adducts **91am/91aq** were isolated in moderate to good yields and with stereoselectivities favouring the *E*-isomers.

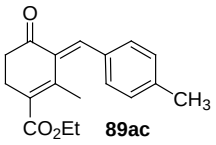
Compared to glycine-catalysis, pyrrolidine-catalysis generated the CS products **89ab-ac**, **89an-ao** with less yields and high *E*-selectivity from **88a** and neutral benzaldehydes **28b-c**, **28n-o** at 25 °C for 12-24 h in DMF as shown in Table 5. But halogenated benzaldehydes **28i-j**/**p** furnished the expected CS products **89ai-aj**/**ap** with **88a** under **2a**-catalysis as similar to **14d**-catalysis in moderate to good yields with *E*-isomer as major (Table 5). Interestingly, CS products **89ak-al** generated with less yields and high *E*-selectivity (>99%) under the pyrrolidine-catalysis from **88a** and heterocyclic aldehydes **28k-l** at 25 °C for 24 h in DMF as shown in Table 5, which is different from the glycine-catalysis results. Reaction of **88a** with *trans*-cinnamaldehyde **28m** under pyrrolidine **2a** catalysis furnished the Michael product **91am** in 65% yield in a 1:1 diastereomeric ratio, which is different from the glycine-catalysis may be due to the nature of **28m** as Michael acceptor under pyrrolidine-catalysis. Formation of Michael adducts from **88a** and α,β-unsaturated aldehyde under pyrrolidine-catalysis is confirmed by one more example as shown in Table 5. Structure and regiochemistry of CS products **89ab-ap** and Michael adducts **91am/91aq** were confirmed by NMR and mass analysis.

Table 5: Synthesis of Chemically Diverse Libraries of 3-Arylidene-Hagemann's Esters **89** via Pyrrolidine-Catalysis[a]

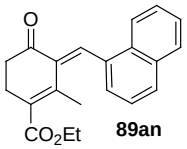




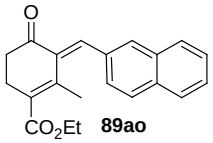
Yield:[b] 55%
Ratio *E*/*Z*[c] = 5.3:1



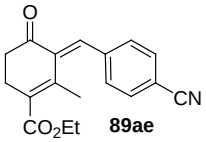
Yield: 35%
E/*Z* = 5.5:1



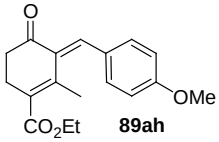
Yield: 55%
E/*Z* = 4.0:1



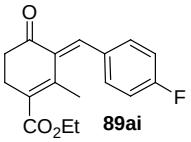
Yield: 50%
E/*Z* = 3.0:1



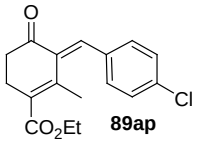
Yield: 85%
E/*Z* = 1.5:1



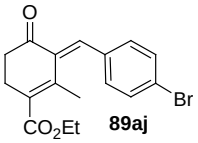
Yield: 25%
E/*Z* = 3.5:1



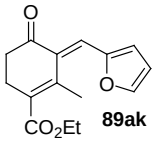
Yield: 60%
E/*Z* = 3.5:1



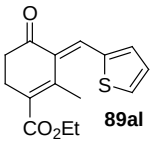
Yield: 50%
E/*Z* = 3.8:1



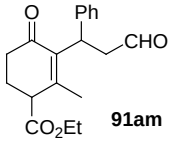
Yield: 35%
E/*Z* = 3.5:1



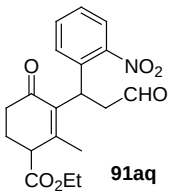
Yield: 45%
E/*Z* = 99:1



Yield: 45%
E/*Z* = 99:1



Yield: 65%
dr = 1:1

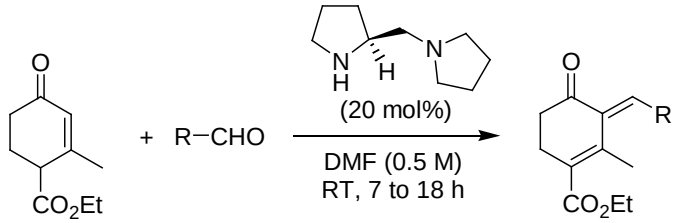


Yield: 65%
dr = 1.2:1

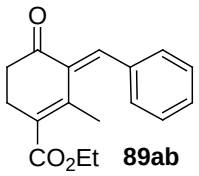
[a] All reactions were carried out in DMF (0.5 M) with the same proportions of Hagemann's ester **88a** and aldehyde **28** in the presence of 20 mol% pyrrolidine. [b] Yield refers to the column-purified product. [c] *E*/*Z* ratio determined by NMR analysis.

3.2.6 Diversity-Oriented Synthesis of Push-Pull Olefins 89ab-as via Diamine-Catalysis: After testing the glycine **14d**- and pyrrolidine **2a**-catalyzed CS reactions with various aldehydes **28b-q**, we further showed interest to screen similar kind of reactions under diamine **2i**-catalysis to look at the high-yielding formation of CS products **89** and CS/IA products **90** (Table 6). A series of neutral, electron-donating and α,β-unsaturated aldehydes **28b-s** and **45d** were reacted with 1.0 equiv. of Hagemann's ester **88a** catalyzed by 20 mol% of (*S*)-1-(2-pyrrolidinyl-methyl)pyrrolidine **2i** at 25 °C for 7-18 h in DMF or DMSO solvents. Interestingly, in these reactions also CS/IA products **90** are not furnished and only the CS products, 3-arylidene Hagemann's esters **89ab-as** were isolated in moderate to good yields with stereoselectivities favouring the *E*-isomers for simple benzaldehydes and favouring the *Z*-isomers for α,β-unsaturated aldehydes without formation of Michael adducts **91** (Table 6). Compared to glycine- and pyrrolidine-catalysis, diamine-catalysis generated the CS products **89ab**, **89ai** and **89ap** with moderate yields and *E*-selectivity from **88a** and neutral/halogenated benzaldehydes **28b**, **28i** and **28p** at 25 °C for 7-18 h in DMF/DMSO as shown in Table 6. But 4-dimethylamino-benzaldehyde **28r** and benzene-1,4-dicarbaldehyde **28s** furnished the only CS products **89ar** and **89as** with **88a** under **2i**-catalysis in good yields with high *E*-selectivity as shown in Table 6. Interestingly, reaction of **88a** with *trans*-cinnamaldehyde **28m** under diamine **2i**-catalysis furnished the CS product (*E*, *Z*, *E*)-triene **89am** in 75% yield with 1:6 *E*/*Z* ratio, which is different from the pyrrolidine-catalysis but similar to the glycine-catalysis. Formation of CS product, (*E*, *Z*, *E*)-triene from **88a** and α,β-unsaturated aldehyde under diamine-catalysis is confirmed by one more example as shown in Table 6. Reaction of 2.0 equiv. of **88a** with 3,3-dimethylacrolein **45d** in DMF at 0 °C for 0.5 h under **2i**-catalysis furnished the selective conjugated (*E*, *Z*, *E*)-triene **89ad** in 60% yield with 1:5 *E*/*Z* ratio (Table 6). Structure and regiochemistry of CS products **89ab-as** were confirmed by ^{1}H NMR, ^{13}C NMR [for example see Fig. 2] and mass analysis and also finally confirmed by X-ray structure analysis on **89ai** as shown in Scheme **2**.[32]

Table 6: Synthesis of Chemically Diverse Libraries of 3-Arylidene-Hagemann's ester **89** via Diamine-Catalysis[a]

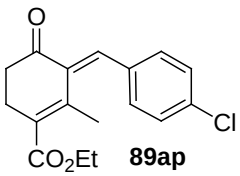


88a **28b-28s & 45d** **89ab-89as**



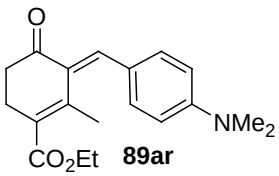
89ab

Yield:[b] 45%
Ratio *E*/*Z*[c] = 3.8:1



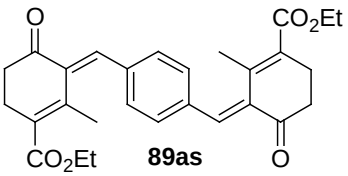
89ap

Yield: 55%
E/*Z* = 2.0:1



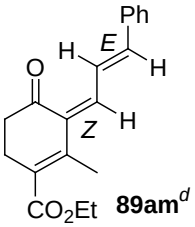
89ar

Yield: 50%
E/*Z* = 99:1



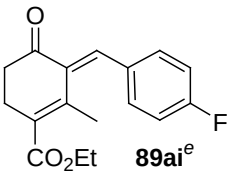
89as

Yield: 75%
E/*Z* = 99:1



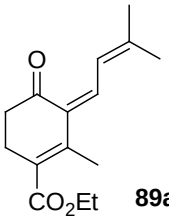
89am[d]

Yield: 75%
E/*Z* = 1:6



89ai[e]

Yield: 50%
E/*Z* = 2.3:1



89ad[f]

Yield: 60%
E/*Z* = 1:5

[a] All reactions were carried out in DMF (0.5 M) with the same proportions of Hagemann's ester **88a** and aldehyde **28** in the presence of 20 mol% diamine **2i**. [b] Yield refers to the column-purified product. [c] *E*/*Z* ratio determined by NMR analysis. [d] Reaction time was 1 h. [e] DMSO was used as the solvent. [f] Hagemann's ester **88a** (1.0 mmol) reacted with aldehyde **45d** (0.5 mmol) in the presence of 20 mol% diamine **2i** at 0 ^{o}C in DMF for 0.5 h.

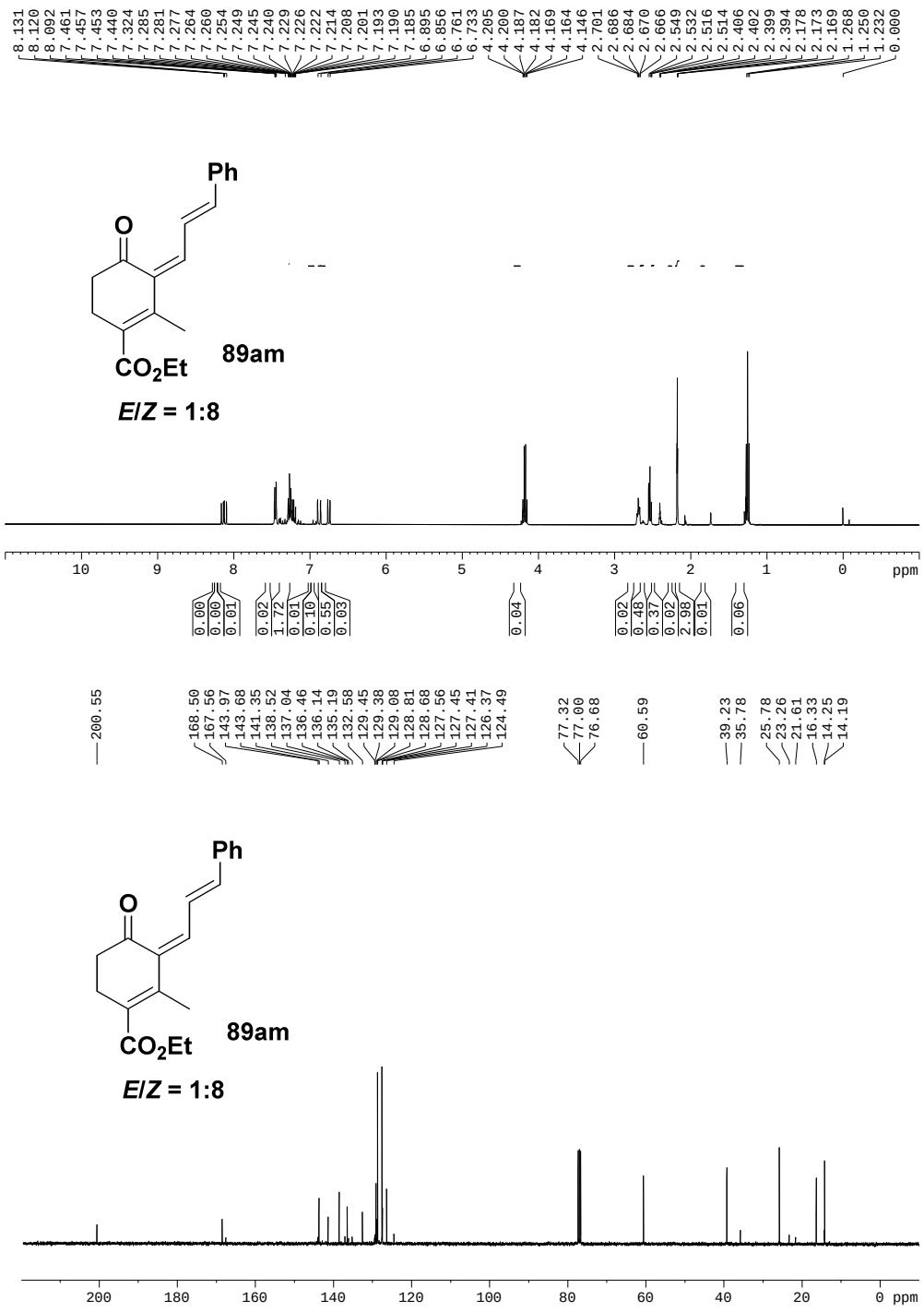
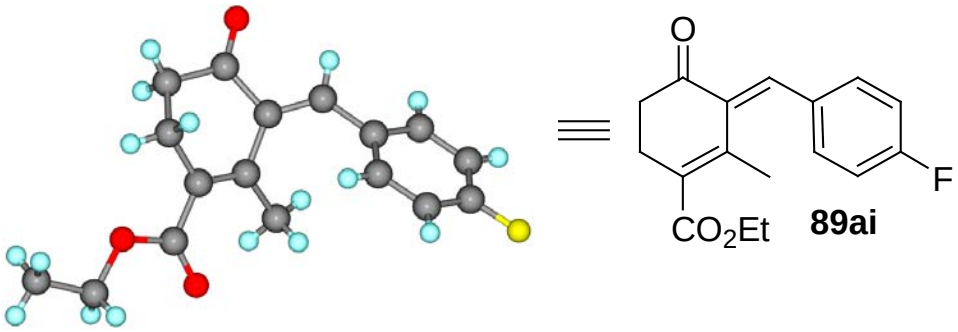


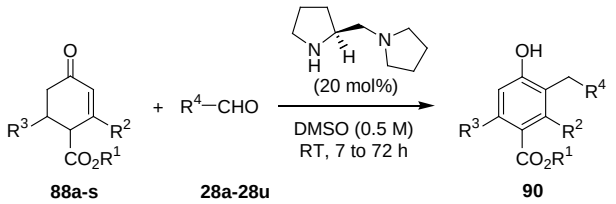
Figure-2: ^{1}H NMR and ^{13}C NMR Spectrum of product **89am**.

Scheme 2: Crystal structure of 3-(4-fluoro-benzylidene)-2-methyl-4-oxo-cyclohex-1-enecarboxylic acid ethyl ester (**89ai**).

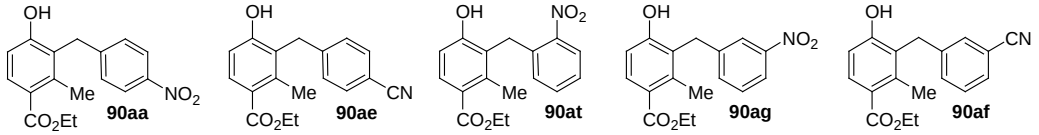


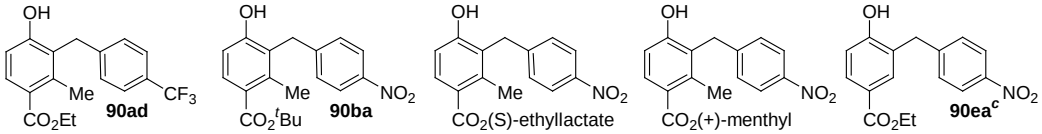
3.2.7 Diversity-Oriented Synthesis of Push-Pull Phenols 90 via Diamine-Catalysis: After thorough investigation of the glycine **14d**-, pyrrolidine **2a**- and diamine **2i**-catalyzed CS reactions of Hagemann's ester **88a** with various aldehydes **28a-s** [Tables 1-6], we further screened only benzaldehydes **28** containing an electron-withdrawing groups with variety of Hagemann's esters **88a-s** under diamine **2i**-catalysis to look at the high-yielding formation of CS/IA products **90** (Table 7). A series of benzaldehydes **28** containing an electron-withdrawing groups and α,β-unsaturation were reacted with 1.0 equiv. of Hagemann's esters **88a-s** catalyzed by 20 mol% of (*S*)-1-(2-pyrrolidinyl-methyl)pyrrolidine **2i** at 25 °C for 7-72 h in DMSO. Interestingly, in all these reactions expected CS/IA products or push-pull phenols **90** were furnished with moderate to very good yields as shown in Table 7. Functionalized push-pull phenols **90** are an important class of compounds, which are widely used as intermediates in the pharmaceuticals.[30f-l]

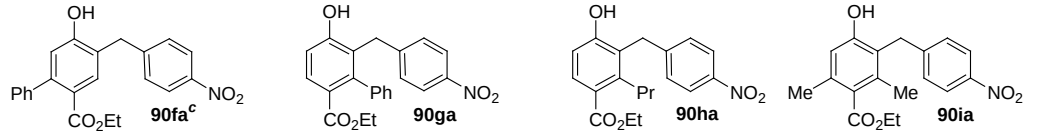
Table 7: Synthesis of Chemically Diverse Libraries of Highly Substituted Phenols **90** via Diamine-Catalysis[a]

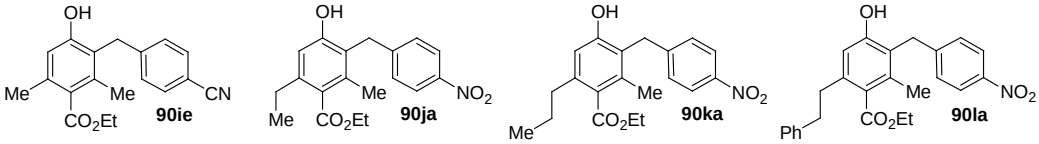


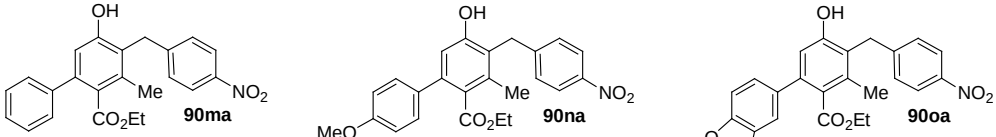
88a-s **28a-28u** **90**











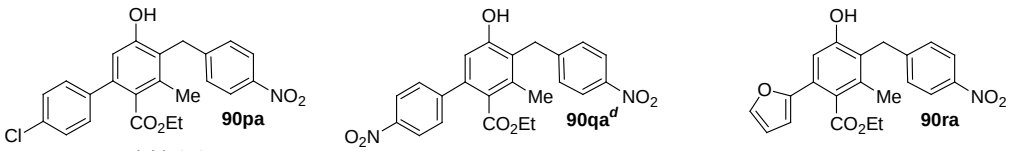
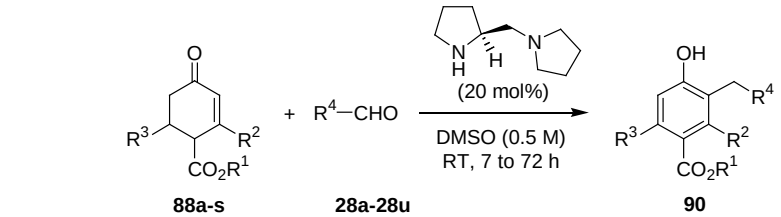
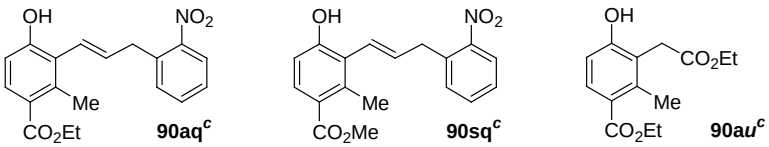


Table 7: Synthesis of Chemically Diverse Libraries of Highly Substituted Phenols **90** via Diamine-Catalysis (Continuation)[a]





[a] All reactions were carried out in DMSO (0.5 M) with the same proportions of Hagemann's ester **88a** and aldehyde **28** in the presence of 20 mol% diamine **2i**. [b] Yield refers to the column-purified product. [c] Hagemann's ester **88** (1.0 mmol) reacted with aldehyde **28** (0.5 mmol) in the presence of 20 mol% diamine **2i** at 25 ^{o}C for 12-24 h. [d] Hagemann's ester **88q** (1.0 mmol) reacted with aldehyde **28a** (0.5 mmol) in the presence of 20 mol% diamine **2i** at 70 ^{o}C for 12 h.

Compounds containing 2-alkyl-push-pull phenols **90** have found pharmaceutical applications as remedies for diabetes **D**, insulin resistance **E**, antiasthmatic LTD4 antagonist ICI-204/219 **F**, lasiodiplodin analogues **G** and also starting materials for the synthesis of natural products as shown in Chart 1.[30f-l] As such, the development of new and more general catalytic methods for their preparation is of significant interest.[31] L-Diamine-catalyzed cascade CS/IA reaction of **88a** with 4-cyanobenzaldehyde **28e** in DMSO at 25 °C for 7 h furnished the expected product **90ae** in 75% yield (Table 7, entry 2). The CS/IA reaction of 2-nitro- and 3-nitrobenzaldehydes **28t/g** with **88a** catalyzed by L-**2i** in DMSO at 25 °C for 7 h furnished the expected **90at/ag** with 75-60% yields respectively as shown in Table 7. After these interesting results, we decided to investigate the scope and limitations of the CS/IA reaction with other two aldehydes containing electron withdrawing groups **28d/f** with **88a** under L-diamine-catalysis at the ambient conditions (Table 7, entries 5-6). Interestingly, CS/IA reaction of 3-

cyanobenzaldehyde **28f** and 4-trifluoromethyl-benzaldehyde **28d** with **88a** under L-diamine-catalysis furnished the expected push-pull phenols **90af** and **90ad** in 60/70% yields respectively as shown in Table 7, entries 5-6.

After these interesting results, we further decided to investigate the scope and limitations of the CS/IA reaction with a range of Hagemann's esters **88a-s** including chiral Hagemann's esters **88c-d**, simple ester **88e**, and 6-substituted Hagemann's esters **88f-r** with 4-nitrobenzaldehyde **28a**, 4-cyanobenzaldehyde **28e**, 3-(2-nitro-phenyl)-propenal **28q** and ethyl glyoxylate **28u** under L-diamine-catalysis in DMSO at the ambient conditions to test the diversity nature of the CS/IA reaction (Table 7). Synthesis of chiral Hagemann's esters **88c**, **88d** described in experimental section as shown in Scheme E1 and Scheme E2.[33] As shown in Table 7, CS/IA reaction of *t*-butyl ester **88b** with **28a** under **2i**-catalysis for 24 h furnished the phenol **90ba** with 75% yield (Table 7, entry 7). Interestingly, CS/IA reaction of 4-nitrobenzaldehyde **28a** with 2.0 equiv. of chiral Hagemann's esters **88c-d** under **2i**-catalysis in DMSO at 25 °C for 24-12 h furnished the chiral push-pull phenols (+)-**90ca** in 80% yield and (–)-**90da** in 90% yield as shown in Table 7, entries 8/9. Diamine-catalyzed CS/IA reaction of 4-nitrobenzaldehyde **28a** with simple Hagemann's esters **88e-f** and **88g-h**[34] in DMSO at 25 °C for 10-24 h furnished the expected push-pull phenols **90ea-ha** in 60-85% yields respectively as shown in Table 7, entries 10-13. Interestingly, CS/IA reaction of 4-nitrobenzaldehyde **28a** with 6-methyl-Hagemann's ester **88i** under **2i**-catalysis in DMSO at 25 °C for 12 h furnished the highly functionalized push-pull phenol **90ia** in 65% yield as shown in Table 7, entry 14. Generality of the diamine-catalyzed CS/IA reaction of 6-substituted Hagemann's esters **88** with 4-nitrobenzaldehyde **28a** or 4-cyanobenzaldehyde **28e** were confirmed by ten more examples with esters **88i-r** containing different functional groups under **2i**-catalysis and furnished the expected highly substituted push-pull phenols **90ia-ra** with 50-80% yields respectively as shown in Table 7. The products structures were confirmed by ^{1}H NMR, ^{13}C NMR [for example see Fig. 3] and mass analysis.

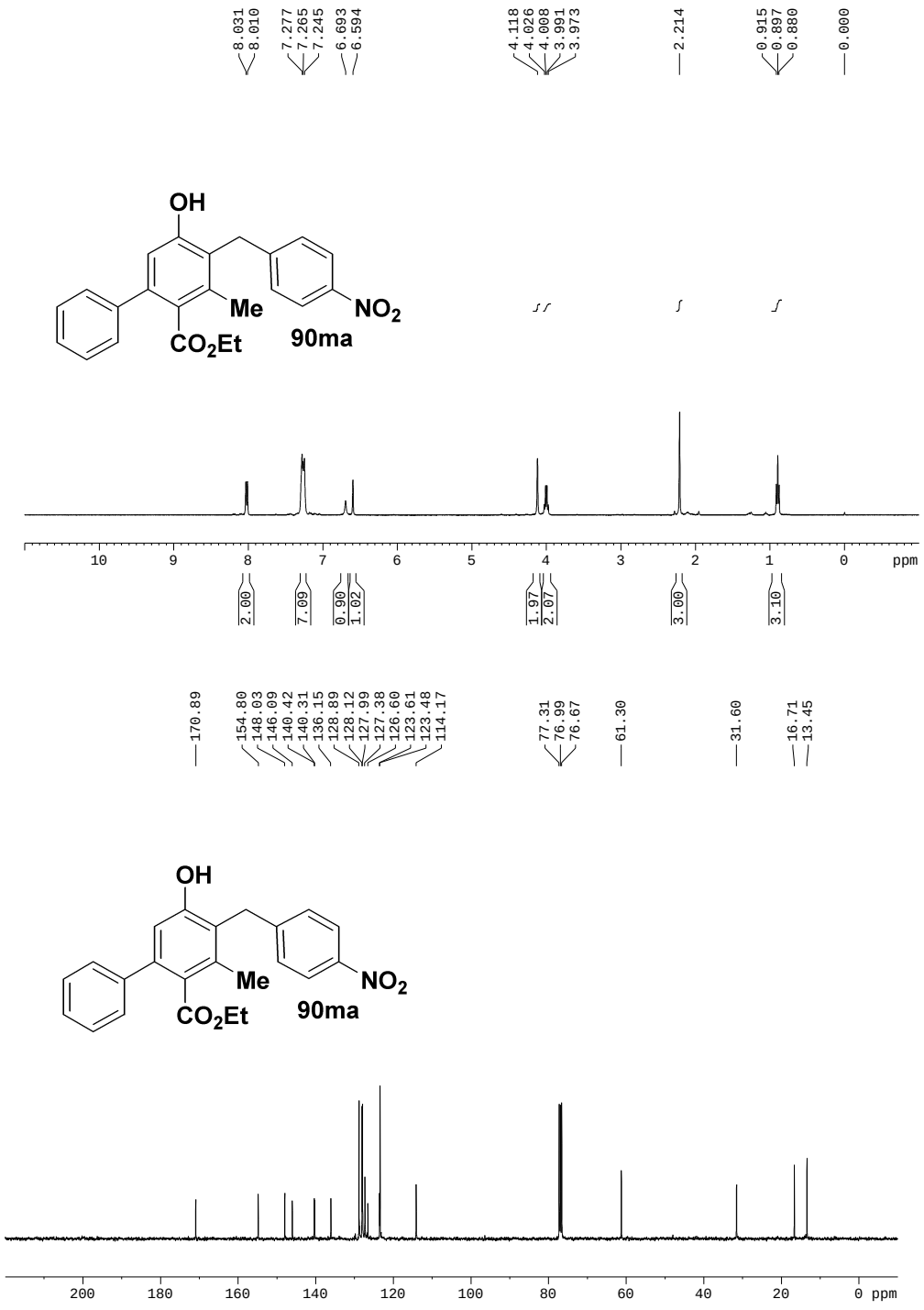


Figure-3: ^{1}H NMR and ^{13}C NMR Spectrum of product **90ma**.

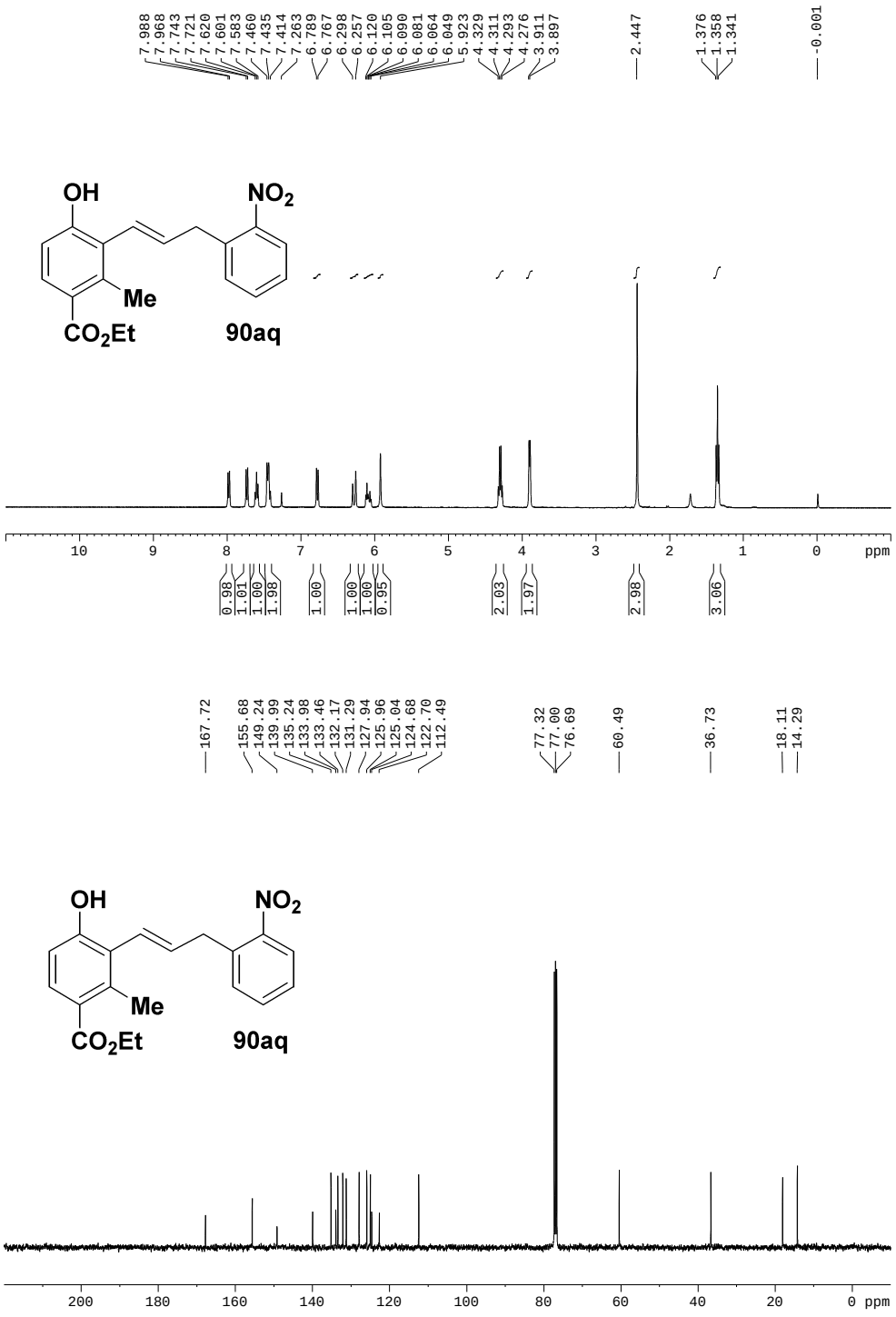
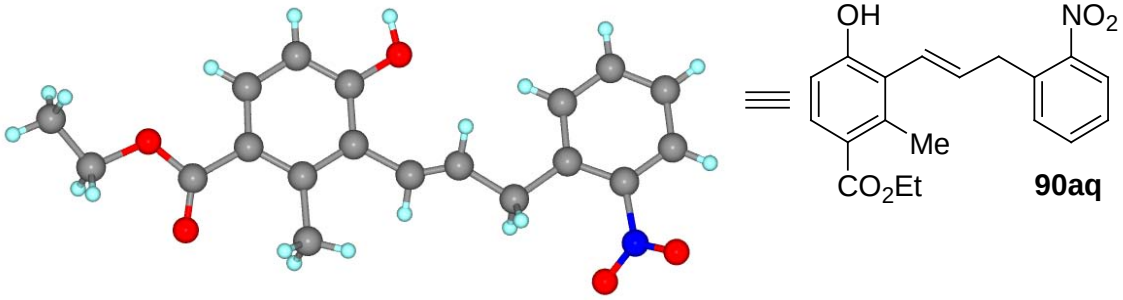


Figure-4: ^{1}H NMR and ^{13}C NMR Spectrum of product **90aq**.

Interestingly, cascade reaction of 3-(2-nitro-phenyl)-propenal **28q** and ethyl glyoxylate **28u** with **88a** under L-diamine-catalysis furnished the novel products **90aq** in 65% yield via CS/IA/I and **90au** in 20% yield via CS/IA reactions as shown in Table 7, entries 25-27. Generality of the **2i**-catalyzed cascade CS/IA/I reaction was confirmed by one more example with **88s** and **28q** as shown in Table 7. Structure and regiochemistry of CS/IA/I products **90aq/sq** were confirmed by ^{1}H NMR, ^{13}C NMR [for example see Fig. 4] and mass analysis and also finally confirmed by X-ray structure analysis on **90aq** as shown in Scheme 3.[35] Presently developed amine-catalyzed CS/IA/I reaction looks novel technology for the *ortho*-vinylation of *in situ* generated functionalized phenols compared to metal mediated *ortho*-vinylation of preformed phenols.[36] Functionalized push-pull phenols **90au-ra** are useful intermediates for the synthesis of analogues of remedies for diabetes **D**, insulin resistance **E**, antiasthmatic LTD4 antagonist ICI-204/219 **F**, lasiodiplodin analogues **G** and also for the synthesis of natural products as shown in Chart 1.[30f-l] This CS/IA technology may be suitable to develop large number of diverse-compounds of **90** to screen and identify the suitable bioactive products.

Scheme 3: Crystal structure of 4-hydroxy-2-methyl-3-[3-(2-nitro-phenyl)-propenyl]-benzoic acid ethyl ester (**90aq**).



3.2.8 Diversity-Oriented Synthesis of Highly Functionalized (E)-1,3-Dienes 92 via Diamine-Catalysis: After thorough investigation of the diamine **2i**-catalyzed CS, CS/IA and CS/IA/I reactions of Hagemann's esters **88a-s** with various aldehydes **28a-u**, we further showed interest to screen aliphatic aldehydes **28v-b'** containing an α-hydrogen with Hagemann's ester **88a** under diamine **2i**-catalysis to look at the effect of electronic factors of substrates on product formation (Table 8). A series of aliphatic aldehydes **28v-b'** containing an α-hydrogen were reacted with 2.0 equiv. of Hagemann's ester **88a** catalyzed by 20 mol% of (*S*)-1-(2-pyrrolidinyl-methyl)pyrrolidine **2i** at 25 °C for 0.5-24 h in DMSO (0.5 M). Surprisingly, in all these reactions unexpected CS/I products **92** were furnished in moderate to very good yields with high selectivity instead of CS products **89** as shown in Table 8.

Interestingly, cascade reaction of optically pure (*R*)-(+)-citronellal **28v** with 2.0 equiv. of Hagemann's ester **88a** under **2i**-catalysis in DMSO at 25 °C for 24 h furnished the chiral functionalized (*E*)-1,3-diene (–)-**92av** in 65% yield with >99:1 ratio of *E*:*Z* isomers and 1:1 ratio of diastereomers as shown in Table 8, entry 1. Unexpected formation of product (–)-**92av** from **88a** and **28v** via **2i**-catalysis can be explained through cascade Claisen-Schmidt/isomerization (CS/I) reactions and further reaction mechanism is discussed in the mechanistic insights. Diamine-catalyzed CS/I reaction of optically pure opposite enantiomer (*S*)-(–)-citronellal **28w** with simple Hagemann's ester **88a** in DMSO at 25 °C for 24 h furnished the chiral functionalized (*E*)-1,3-diene (+)-**92aw** in 65% yield with >99:1 ratio of *E*:*Z* isomers and 1:1 ratio of diastereomers as shown in Table 8, entry 2. Generality of the diamine-catalyzed CS/I reaction of Hagemann's ester **88a** with chiral aliphatic aldehyde[37] were confirmed by one more example with dimethyl 2-(3-oxo-1-phenyl-propyl)-malonate [93% ee, (–)-**28x**] containing an α-hydrogen under **2i**-catalysis and furnished the expected highly substituted chiral (*E*)-1,3-diene (+)-**92ax** in 50% yield with >99:1 ratio of *E*:*Z* isomers and 1:1 ratio of diastereomers as shown in Table 8, entry 3.

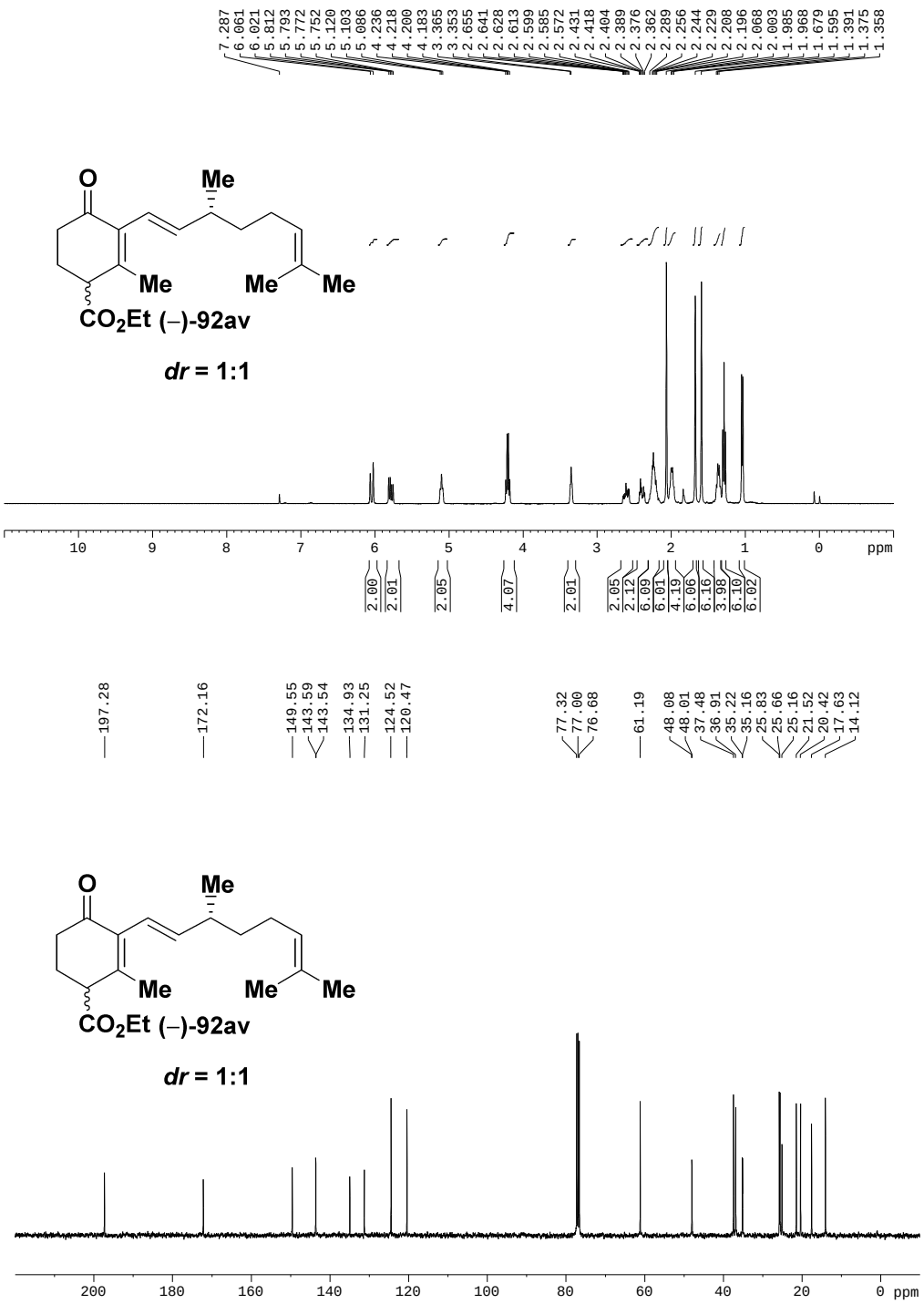
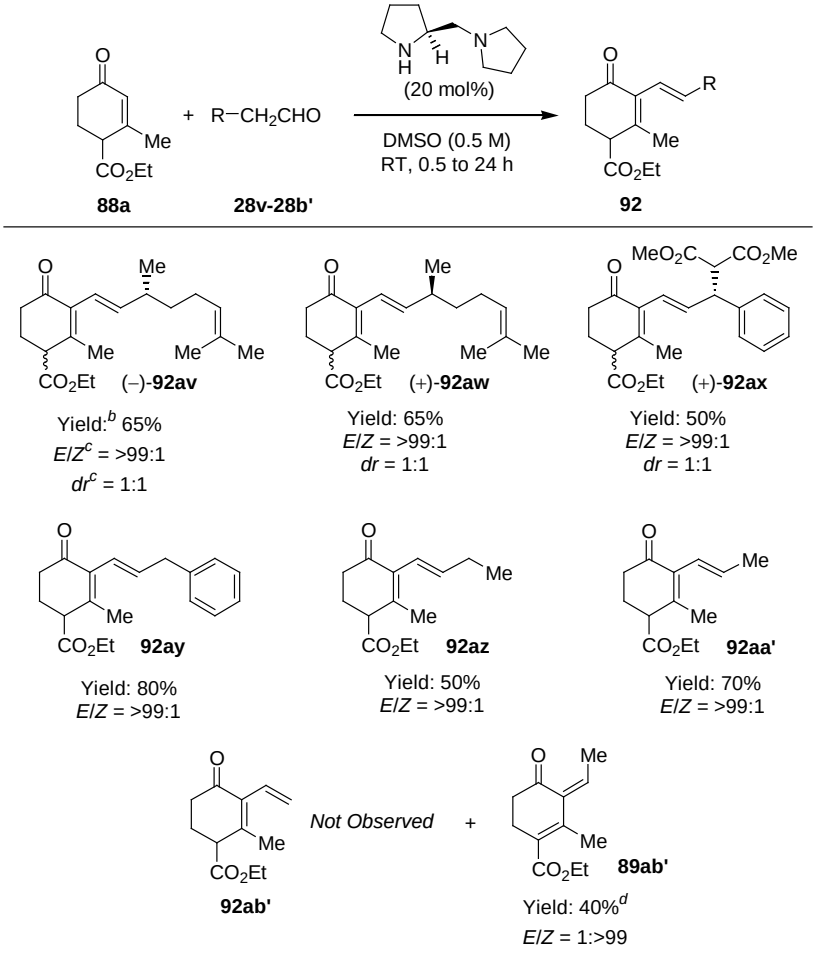


Figure-5: ^{1}H NMR and ^{13}C NMR Spectrum of product **92av**.

After successful demonstration of diamine-catalyzed cascade CS/I reaction of **88a** with chiral aldehydes **28v-x**, we further investigated the scope and limitations of the cascade CS/I reaction with a range of achiral aliphatic aldehydes **28y-b'** containing an α-hydrogen under L-diamine-catalysis in DMSO at the ambient conditions to test the diversity nature of the CS/I reaction (Table 8). The products structures were confirmed by ^{1}H NMR, ^{13}C NMR [for example see Fig. 5] and mass analysis.

Table 8: Synthesis of Chemically Diverse Libraries of 1,3-Dienes **92** via Diamine-Catalysis[a]



[a] Hagemann's ester **88a** (1.0 mmol) reacted with aldehyde **28v-28b'** (0.5 mmol) in the presence of 20 mol% diamine **2i** at 25 ^{o}C in DMSO for 0.5 to 24 h. [b] Yield refers to the column-purified product. [c] *E*/*Z* and *dr* ratio determined by NMR analysis. [d] Reaction stirred at 0 ^{o}C in DMF for 0.5 h.

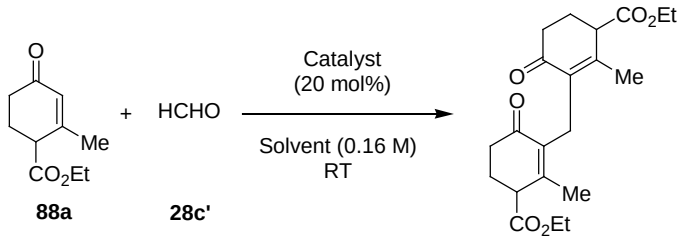
Cascade CS/I reaction of ester **88a** with 3-phenyl-propionaldehyde **28y** under **2i**-catalysis for 17 h furnished the achiral (*E*)-1,3-diene **92ay** in 80% yield with >99:1 ratio of *E*:*Z* isomers as shown in Table 8, entry 4. In a similar manner, cascade CS/I reaction of butyraldehyde **28z** and propionaldehyde **28a'** with 2.0 equiv. of Hagemann's ester **88a** under **2i**-catalysis in DMSO at 25 °C for 24/12 h furnished the achiral (*E*)-1,3-dienes **92az** in 50% yield with >99:1 ratio of *E*:*Z* isomers and **92aa'** in 70% yield with >99:1 ratio of *E*:*Z* isomers, respectively as shown in Table 8, entries 5/6. Interestingly, cascade CS/I reaction of Hagemann's ester **88a** with acetaldehyde **28b'** under **2i**-catalysis in DMSO is not clean reaction, but same reaction in DMF at 0 °C for 0.5 h furnished the only CS product **89ab'** in 40% yield with 1:>99 ratio of *E*:*Z* isomers instead of expected 1,3-diene **92ab'** as shown in Table 8, entry 7.

Amine-induced cascade CS/I reaction is first time to observe and certainly this CS/I technology suitable to develop large number of diverse-compounds of **92** to screen and identify the suitable intermediates for the bioactive and natural product synthesis.

3.2.9 Diversity-Oriented Synthesis of Highly Functionalized bis-Enones 93 via Piperidine-Catalysis: After the investigation of the amino acid **14** or amine **2** catalyzed CS, CS/IA, CS/IA/I and CS/I reactions of Hagemann's esters **88a-s** with various aldehydes **28a-b'**, we further interested to screen simple formaldehyde **28c'** with Hagemann's ester **88a** under amine **2**-catalysis (Table 9 and Scheme 4). Interestingly, reaction of 37% aqueous formaldehyde **28c'** with 2.0 equiv. of Hagemann's ester **88a** under proline **14a**-catalysis in DMSO at 25 °C for 24 h furnished the functionalized *bis*-enone **93ac'** in 55% yield with >99% de as shown in Table 9, entry 1. Unexpected formation of product **93ac'** from **88a** and **28c'** via **14a**-catalysis can be explained through cascade Claisen-Schmidt/Michael (CS/M) reactions and further information on the reaction mechanism is discussed in the mechanistic insights. Functionalized *bis*-enones **93** would be suitable intermediates for the synthesis of

terpenoid natural products[38] and for the development of high-yielding one-pot synthesis of **93** *via* amine-catalysis is very much needed.

Table 9: Optimization of the Direct Amine-Catalyzed Cascade Claisen-Schmidt and Michael reaction of **88a** and **28c'**[a]



88a **28c'** **93ac'**

entry	catalyst (20 mol%)	solvent (0.16 M)	time (h)	yield (%)[b] **93ac'**
1	proline **14a**	DMSO	24	55
2	glycine **14d**	DMSO	24	55
3[c]	pyrrolidine **2a**	DMSO	4	65
4	**pyrrolidine 2a**	**DMSO**	**1**	**76**
5	pyrrolidine **2a**	DMF	1	70
6	**piperidine 2b**	**DMSO**	**1**	**80**
7	diamine **2i**	DMSO	1	72

[a] Reactions were carried out in solvent (0.16 M) with the 2.0 equiv. of Hagemann's ester **88a** to 37% aqueous formaldehyde **28c'** in the presence of 20 mol% catalyst. [b] Yield refers to the column-purified product. [c] 1:1 ratio of ester **88a** and 37% aqueous formaldehyde **28c'** was used.

For the high-yielding one-pot synthesis of *bis*-enone **93ac'** from simple substrates **88a** and **28c'**, we further screened catalysts and solvent effect on the cascade CS/M reaction as shown in Table 9. The cascade CS/M reaction of **88a** and **28c'** under glycine **14d**-catalysis in DMSO also as similar to **14a**-catalysis, but the same cascade reaction under pyrrolidine **2a**-catalysis furnished the product **93ac'** with improved yield (76%) as shown in Table 9, entries 2-4.

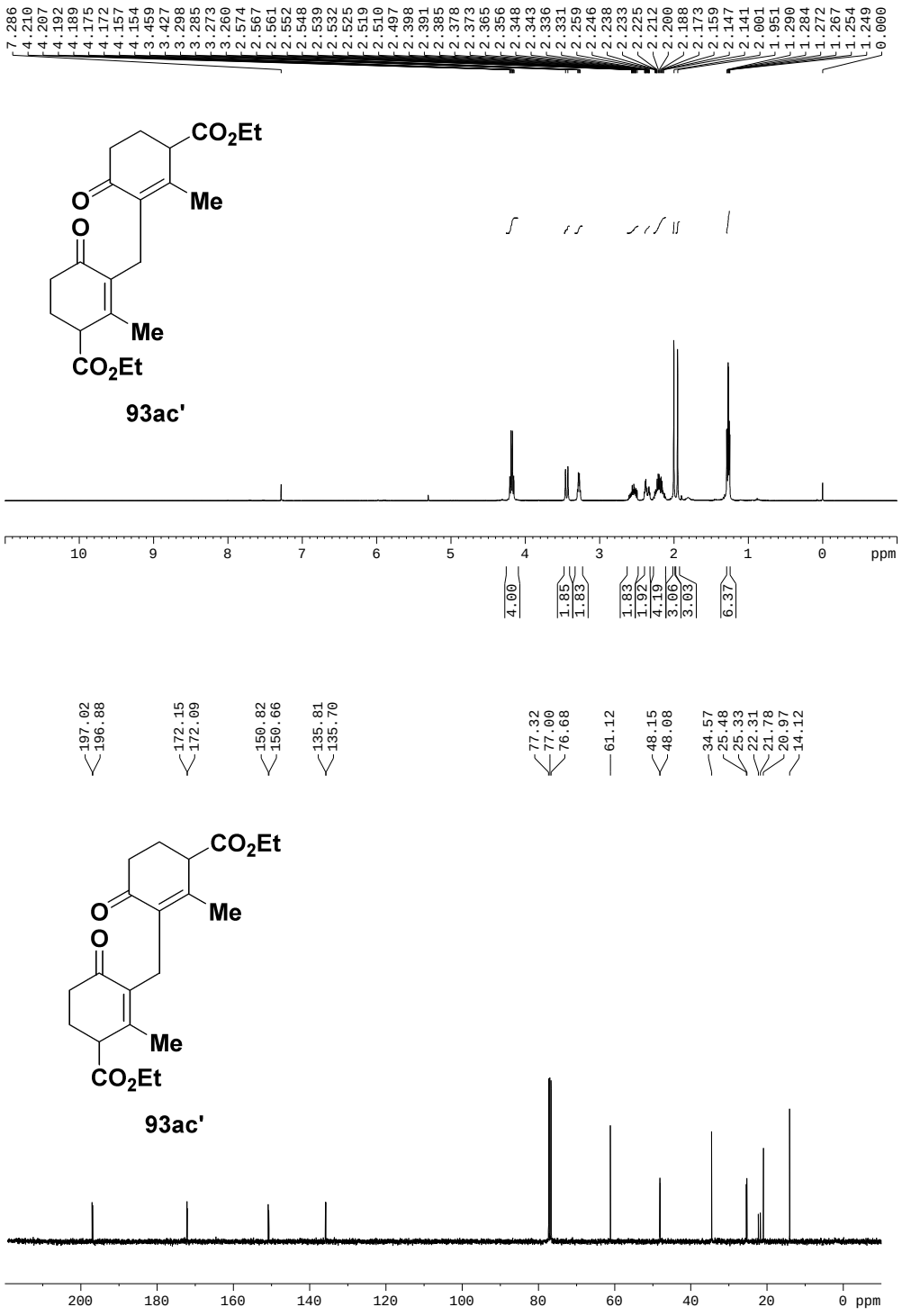
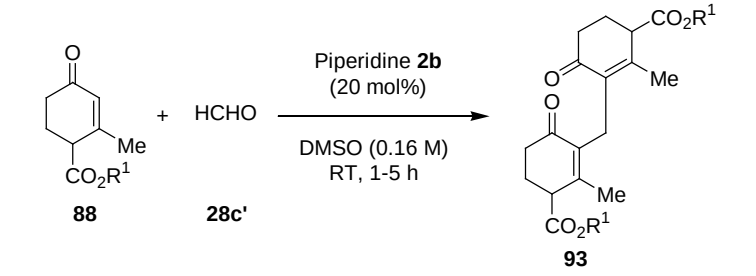
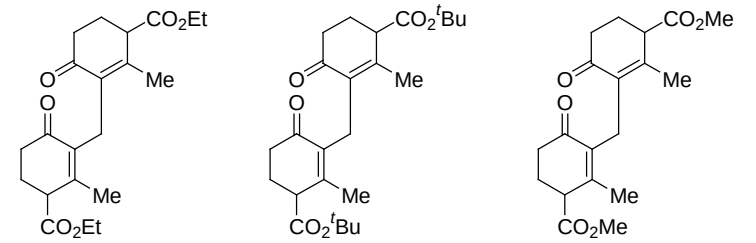


Figure-6: ^{1}H NMR and ^{13}C NMR Spectrum of product **93ac'**.

DMSO looks better solvent for cascade CS/M reaction of **88a** and **28c'** compared to DMF under **2a**-catalysis (Table 9, entry 5). The CS/M reaction yield is increased to 80% under the piperidine **2b**-catalysis in DMSO for 1 h at 25 °C as shown in Table 9, entry 6. Diamine-catalyzed CS/M reaction of **28c'** with **88a** in DMSO at 25 °C for 1 h furnished the functionalized *bis*-enone **93ac'** in 72% yield with >99% de, which is not superior compared to piperidine-catalysis as shown in Table 9, entry 7. The optimized reaction conditions for *bis*-enone synthesis involved piperidine **2b**-catalysis at 25 °C in DMSO with 2 equiv. of **88a** and **28c'**, which furnished the cascade CS/M product **93ac'** in 80% yield with >99% de (Table 9, entry 6).

Scheme 4: Synthesis of Dienones **93** via Direct Amine-Catalyzed Cascade Claisen-Schmidt/Michael reactions[a,b]





93ac' (80%) dr: >99:1 | **93bc'** (20%) dr: >99:1 | **93sc'** (60%) dr: >99:1

[a] See Experimental Section. [b] Yield refers to the column purified product.

Generality of the piperidine-catalyzed CS/M reaction of formaldehyde **28c'** with Hagemann's esters **88** were confirmed by two more examples with *t*-butyl ester **88b** and methyl ester **88s** under **2b**-catalysis and furnished the expected highly substituted *bis*-

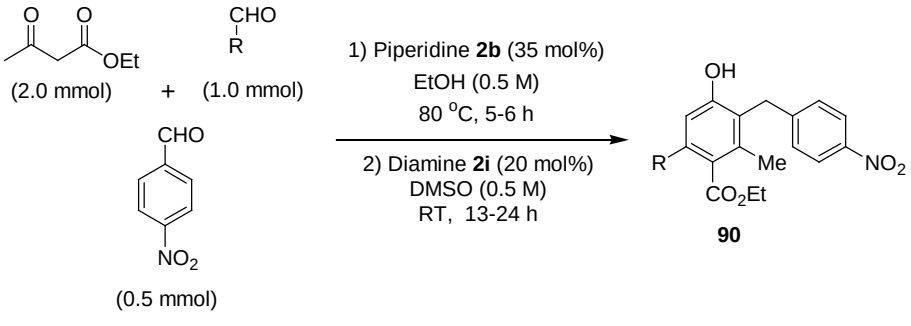
enones **93bc'** in 20% yield with >99% de and **93sc'** in 60% yield with >99% de as shown in Scheme 4. The products structures were confirmed by ^{1}H NMR, ^{13}C NMR [for example see Fig. 6] and mass analysis.

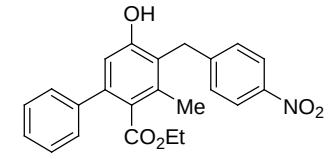
3.2.10 Applications of the Push-Pull Dienamine Chemistry

A. Development of Sequential One-pot Combination of Cascade Reactions based on the CS/IA Platform: Functionalized phenols **90** are an important class of compounds, which are widely used as intermediates in the pharmaceuticals and natural product synthesis as shown in Chart 1.[30] As such, the development of new and more general one-pot catalytic methods for their high-yielding preparation is of significant interest.[31] Hagemann's esters **88a-s** were synthesized in good yields with minor modifications of known methods of direct piperidine- or KO^{t}Bu-catalyzed cascade Knoevenagel/Michael/aldol condensation/decarboxylation (K/M/A/DC) reactions of alkyl acetoacetates and aldehydes (Table 10).[1b] Herein, we utilized the direct sequential combination of piperidine-catalyzed cascade K/M/A/DC and diamine-catalyzed cascade CS/IA of ethyl acetoacetate, aldehydes and 4-nitrobenzaldehyde to furnish the highly functionalized phenols **90** with high yields in one-pot as shown in Table 10.

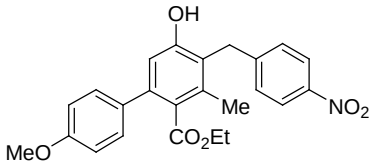
Cascade K/M/A/DC reaction of two equiv. of ethyl acetoacetate and benzaldehyde under piperidine-catalysis in EtOH at 80 °C for 5-6 h furnished the expected Hagemann's ester **88m** with >99% conversion, which on *in situ* treatment with 4-nitrobenzaldehyde **28a** at 25 °C in same solvent didn't furnished the expected product **90ma** in good yield; but removing the solvent EtOH by vacuum pump and adding solvent DMSO, 20 mol% of diamine **2i** and 4-nitrobenzaldehyde **28a** to the reaction mixture of cascade K/M/A/DC furnished the expected product **90ma** in 80% yield as shown in Table 10, entry 1.

Table 10: Sequential Combination of Cascade Knoevenagel/Michael/Aldol Condenasation/Decarboxylation and Cascade Claisen-Schmidt/Iso-aromatization Reactions in One-Pot[a,b]

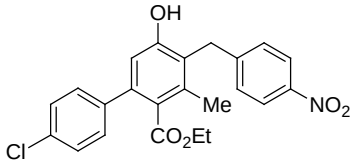




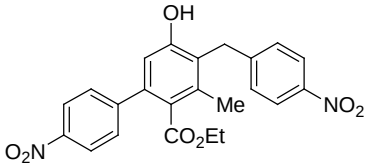
80% (**90ma**)



70% (**90na**)



60% (**90pa**)



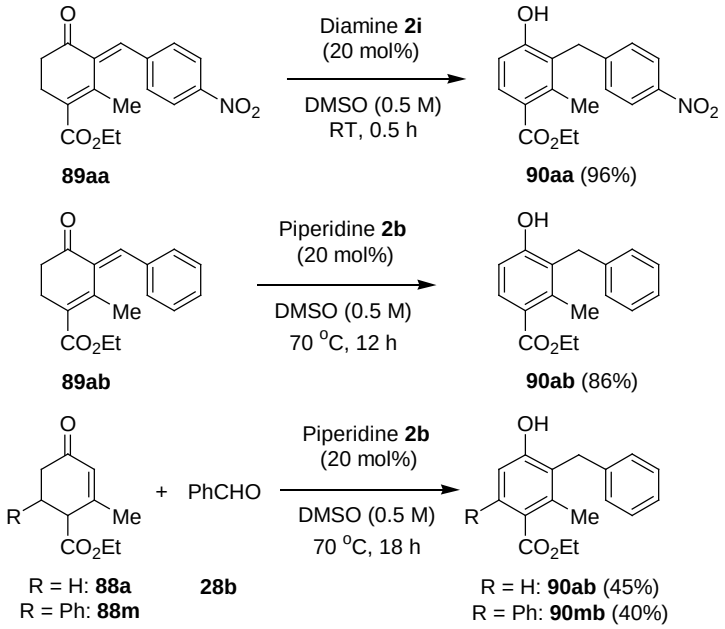
60% (**90qa**)

[a] See Experimental Section. [b] Yield refers to the column purified product.

Successful sequential one-pot combination of two cascade K/M/A/DC and CS/IA reactions under piperidine-/diamine-catalysis was demonstrated by three more examples with good yields as shown in Table 10 and this one-pot synthetic strategy will show much impact on the synthesis of functionalized phenols **90** from simple substrates.

B. Base-Catalyzed Iso-aromatization of CS Products: After successful synthesis of functionalized push-pull phenols **90** from Hagemann's esters **88a-s** and benzaldehydes

Scheme 5: Controlled Experiments on Base-induced Iso-aromatization of 3-Arylidene-Hagemann's ester **89** via Amine-Catalysis



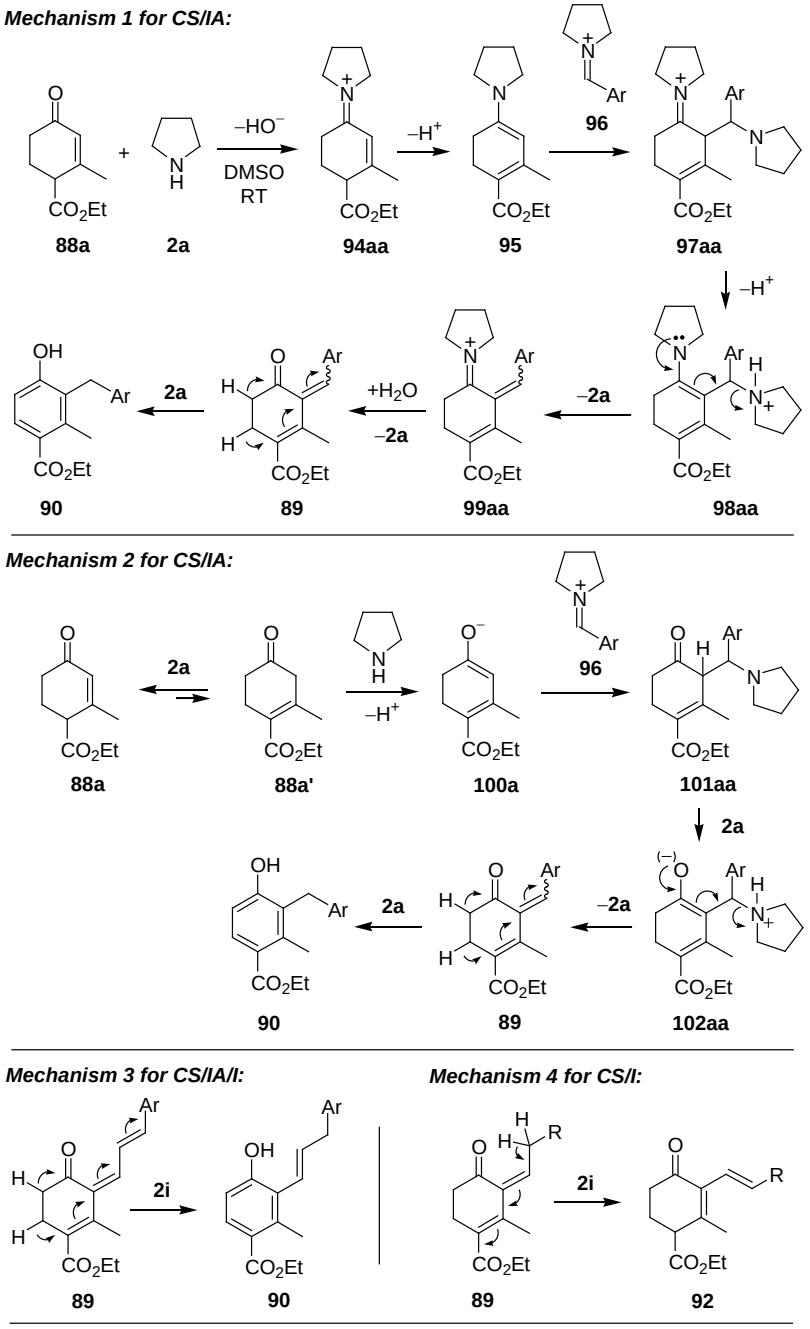
28 containing an electron-withdrawing group under diamine-catalysis, we thought of testing the how much basic nature of amine **2** and electronic nature of substrates **88**/**28** will control the iso-aromatization of CS products **89** as shown in Scheme 5. Interestingly, treatment of pure CS product **89aa** with 20 mol% of diamine **2i** in DMSO at 25 °C for 0.5 h furnished the phenol **90aa** in 96% yield via iso-aromatization as shown in Scheme 5. In a similar manner, treatment of pure CS product **89ab** with 20 mol% of piperidine **2b** in DMSO at 70 °C for 12 h furnished the phenol **90ab** in 86% yield via iso-aromatization as shown in Scheme 5. These results suggesting that both basic nature of amine **2**, electronic nature of substrates **88**/**28** and also reaction temperature is important for the iso-aromatization of CS products **89**.

With an efficient piperidine-catalyzed iso-aromatization protocol in hand, we continued our investigation for the synthesis of functionalized phenols **90** from Hagemann's esters **88a**/**m** and benzaldehyde **28b** under piperidine-catalysis in DMSO at 70 °C for 18 h through cascade CS/IA reactions as shown in Scheme 5. Cascade

products **90ab** and **90mb** were furnished in moderate yields by without showing much of electronic factors in CS/IA reaction as shown in Scheme 5. Functionalized phenols are of considerable importance in a variety of industries. These compounds **90** are widespread elements in natural products and have attracted much attention from a wide area of science, including physical chemistry, medicinal chemistry, natural product chemistry, synthetic organic chemistry and polymer science.[30] As such, the development of new and more general catalytic methods for their preparation is of significant interest and our presently developed cascade chemistry will be useful to develop library of substituted phenols in very good yields with high selectivity.

3.2.11 Mechanistic Insights: The possible reaction mechanisms for the synthesis of push-pull olefins (3-arylidene-Hagemann's ester) **89**, push-pull phenols **90** and (*E*)-1,3-dienes **92** via dienamine-catalysis are illustrated in Schemes 6-7 and Figure 8. First, reaction of amino acids (proline **14a**, phenylalanine **14c** or glycine **14d**) or amines (pyrrolidine **2a**, piperidine **2b**, or (*S*)-1-(2-pyrrolidinyl-methyl)pyrrolidine **2i**) with the aldehyde **28** generates the imine cation **96**, an excellent electrophile that undergoes Mannich type reactions with the *in situ* generated push-pull dienamine **103** & **95** or dienolate **100a** of Hagemann's ester **88a** to generate Mannich products **97** and **101**, respectively as shown in mechanism 1 and 2 of Scheme 6 (for the clarity purpose, we represented **2a** as catalyst). Elimination reaction of amines **98** and **102** under basic conditions would furnish *E*/*Z* mixtures of push-pull olefin **89**. Base-induced, electronically- and temperature-controlled iso-aromatization (IA) of the CS product **89** would then give push-pull phenol **90** as shown in mechanism 1 and 2 of Scheme 6. The formation of imine ion **96** and CS product **89** via Mannich and amine elimination type reactions supports our hypothesis that aldol products did not form in these reactions and also formation of the highly reactive push-pull dienamines **103** and **95** were established through NMR experiments as shown in Scheme 7 and Figure 8. We favor mechanism 1 based on *in situ* NMR experiments. The products structures were confirmed by ^{1}H NMR, ^{13}C NMR [for example see Fig. 7] and mass analysis.

Scheme 6: Proposed Reaction Mechanisms for Push-Pull Dienamine Chemistry



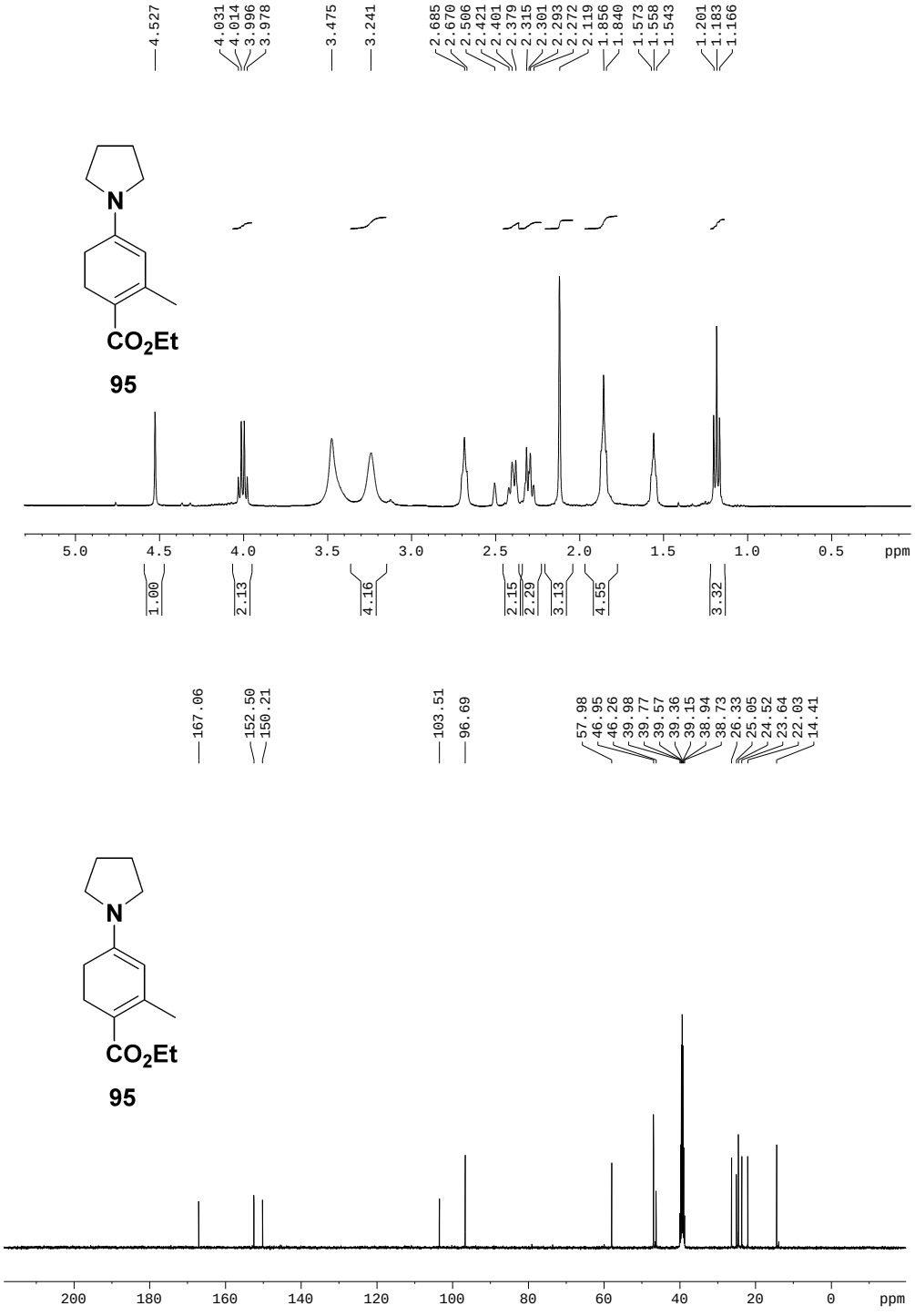


Figure-7: ^{1}H NMR and ^{13}C NMR Spectrum of product **95**.

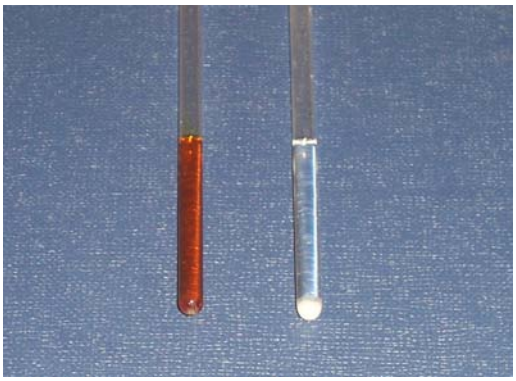
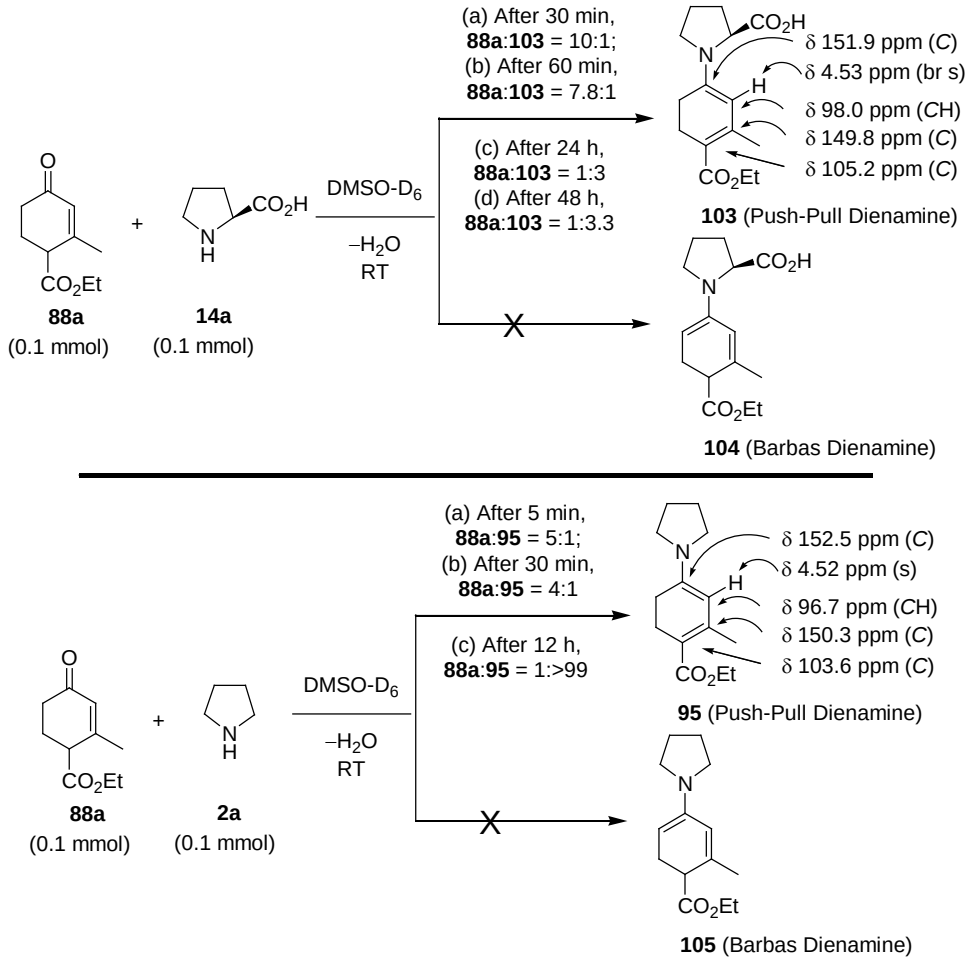


Figure-8: Picture of NMR samples recorded after three days [first NMR tube representing the mixture of **88a** and **14a** in DMSO-D_6 and second NMR tube representing the only undissolved catalyst **14a** in DMSO-D_6].

As shown in Scheme 7, *in situ* generation of novel push-pull dienamine **103** from **88a** and **14a** is slow process as compared to **95** from **88a** and **2a** and similar kind of reactivity patron represented in their reactions also as shown in Tables 1-10. Highly selective *in situ* formation of push-pull dienamines **103** and **95** over the Barbas dienamines (2-amino-1,3-butadienes)[14,15b,19,21,23,25,39] **104** and **105** were established based on NMR and mass analysis as shown in Scheme 7. Presently discovered relatively stable push-pull dienamine **103** formation from Hagemann's ester **88a** and amino acid, L-proline **14a** is very good supportive to the recently proposed enamine mechanism in proline-catalyzed asymmetric reactions[8,40] as revealed in Scheme 7 and Figure 8. Next, the possible mechanism for regioselective synthesis of cascade CS/IA/I and CS/I products, *ortho*-vinylated phenols **90** and (*E*)-1,3-dienes **92** through reaction of Hagemann's ester **88a**, aldehydes **28** and diamine **2i** is illustrated in mechanism 3 and 4 of Scheme 6. Treatment of *in situ* generated CS product, push-pull trienone (arylidene-Hagemann's ester) **89** under the amine-catalysis furnished the *ortho*-vinylated phenol **90** via IA/I reaction. In a similar manner, reaction of *in situ* generated CS product, push-pull dienone (alkylidene-Hagemann's ester) **89** under the base-

catalysis furnished the unexpected (*E*)-1,3-dienes **92** via I reaction as shown in Scheme 6.

Scheme 7: NMR Experiment for the Detection of *In Situ* Generated Push-Pull Dienamines.



These two kinds of isomerizations (I) on **89** through diamine-catalysis were completely controlled by electronic factors and acidic nature of hydrogen's as shown in Scheme 6.

3.3 CONCLUSION

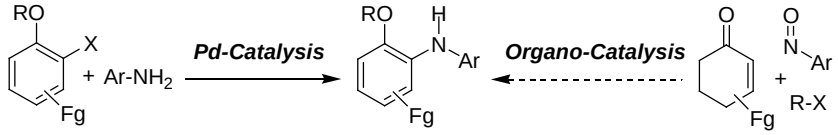
In this chapter, we have developed the sequential one-pot combination of amino acid, amine catalyzed direct cascade CS, CS/IA, CS/IA/I, CS/I, M, CS/M, K/M/A/DC/CS/IA reactions from simple substrates. This experimentally simple cascade approach can be used to construct highly substituted push-pull olefins and phenols with good yields in a selective fashion. We have demonstrated the *in situ* generation and application of novel push-pull dienamines in sequential cascade chemistry.

4. ORGANOCATALYTIC CASCADE REACTIONS BASED ON PUSH-PULL DIENAMINE PLATFORM: SYNTHESIS OF HIGHLY SUBSTITUTED ANILINES

4.1 INTRODUCTION

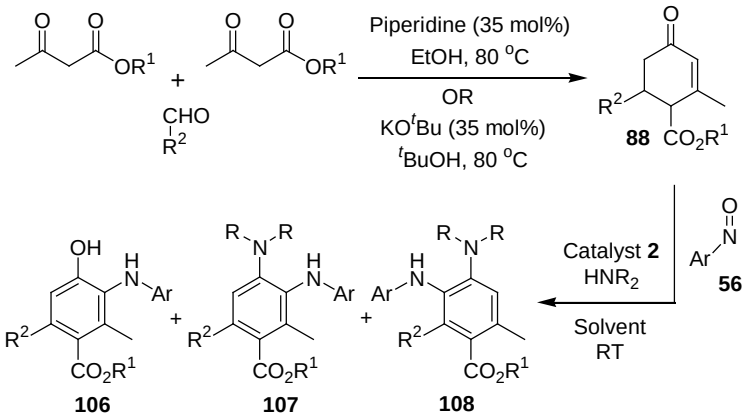
Aryl-amines are of considerable importance in a variety of industries. As such, the development of new and more general methods for their preparation is of significant interest.[41] Recently palladium catalysis emerging for the reactions of aryl halides with primary and secondary amines under the presence of strong base to provide general route to a variety of aryl-amines in good yields (Scheme 8).[42]

Scheme 8: Synthesis of Highly Substituted Anilines



Herein, we discovered a metal-free, novel and green technology for the synthesis of highly substituted o-hydroxydiarylamines, o-pyrrolidin-1-yl-diarylamines and o-alkyloxydiarylamines by using direct organocatalytic cascade enamine amination/iso-aromatization (EA/IA) and enamine amination/iso-aromatization/alkylation (EA/IA/A) reactions from commercially available enones, nitrosobenzenes and alkyl halides (Scheme 8). Direct combination of amine-catalyzed cascade Knoevenagel/Michael/aldol condensation/decarboxylation (K/M/A/DC) and cascade enamine amination/iso-aromatization (EA/IA) of alkyl acetoacetates, aldehydes and nitrosoarenes was developed in one-pot as shown in Scheme 9. o-Hydroxydiarylamines are useful materials as additives for rubbers and plastics, antioxidants, antibacterial activity, anti-fibrillant activiy and hair dyeing.[43]

Scheme 9: Organocatalytic Cascade Approach to the Synthesis of Highly Substituted Anilines

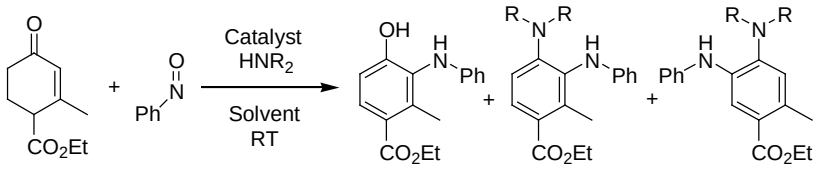


In continuation of our discovery of in situ generation and application of novel push-pull dienamines[1a] in tandem reactions, we initiated our studies of the cascade EA/IA reaction by screening a number of known and novel organocatalysts for the amination of a variety of Hagemann's esters **88** with different nitrosoarenes **56** as shown in Scheme 9. For developing this novel cascade EA/IA reaction, we need a library of Hagemann's esters **88** and we synthesized these esters **88** in good yields with minor modifications of known methods of direct piperidine- or KO^{t}Bu-catalyzed cascade K/M/A/DC reactions (Scheme 9).[44]

4.2 RESULTS AND DISCUSSION

We initiated our studies of the cascade EA/IA reaction by screening a number of known and novel organocatalysts for the amination of Hagemann's ester **88a** by 0.5 to 1.0 equivalents of nitrosobenzene **56a** as shown in Table 11.[45] Proline catalyzed the formation of o-hydroxydiarylamine **106aa** in moderate yields in DMSO and DMF solvents (Table 11, entries 1 and 2). Interestingly, catalyst diamine generated the cascade product **106aa** in very good yield in DMSO (Table 11, entry 3).

Table 11: Optimization of Direct Organocatalytic Cascade Synthesis of o-Hydroxydiarylamines[a]



88a **56a** **106aa** **107aa** **108aa**

entry	catalyst (20 mol%)	solvent (0.3 M)	H. ester **88a** (eq.)	time (h)	products yield (%)[b]		
					106aa	**107aa**	**108aa**
1	Proline	DMSO	1.0	6	46	–	–
2	Proline	DMF	1.0	6	32	–	–
3	**Diamine**[c]	**DMSO**	**2.0**	**1**	**90**	**–**	**–**
4	Glycine	DMSO	2.0	36	30	–	–
5	Piperidine	DMSO	2.0	1	87	–	–
6	**Morpholine**	**DMSO**	**2.0**	**1**	**88**	**–**	**–**
7	Benzylamine	DMSO	2.0	1	83	–	–
8	**Pyrrolidine**	**DMSO**	**2.0**	**1**	**88**	**4**	**4**
9[d]	**Pyrrolidine**	**DMSO**	**2.0**	**1**	**85**	**2**	**2**
10	Pyrrolidine	DMSO	1.0	1	70	2	2
11	Pyrrolidine	CH_3CN	2.0	10	40	10	10
12	Pyrrolidine	EtOH	2.0	10	35	10	10
13	**106aa** (5 mol%)	DMSO	2.0	72	35	–	–
14	–	DMSO	2.0	72	–	–	–

[a] Reactions were carried out in solvent (0.3 M) with 1.0 to 2.0 equiv. of **88a** relative to the **56a** in the presence of 20 mol% of catalyst. [b] Yield refers to column purified product. [c] (s)-1-(2-pyrrolidinylmethyl)pyrrolidine. [d] 5 mol% of pyrrolidine used.

Secondary-amines like piperidine and morpholine catalysts also furnished the cascade product **106aa** in very good yields with excellent regio-selectivity in DMSO solvent (entries 5 and 6). Primary amine, benzyl amine also catalyzed the formation of cascade product **106aa** in good yield (entry 7). Simple amine, pyrrolidine catalyzed the cascade EA/IA reaction to produce **106aa** in 88% yield, which was accompanied by 1:1 regio isomers of o-pyrrolidin-1-yl-diarylamines **107aa** and **108aa** in 8% yield (entry 8). Amine-catalyzed cascade EA/IA reactions are solvent dependent and also auto-catalyzed reactions as shown in Table 11, entries 10 to 14. 5 mol% of **106aa**-Catalyzed the cascade EA/IA reaction of **88a** and **56a** to produce, product **106aa** in 35% yield.

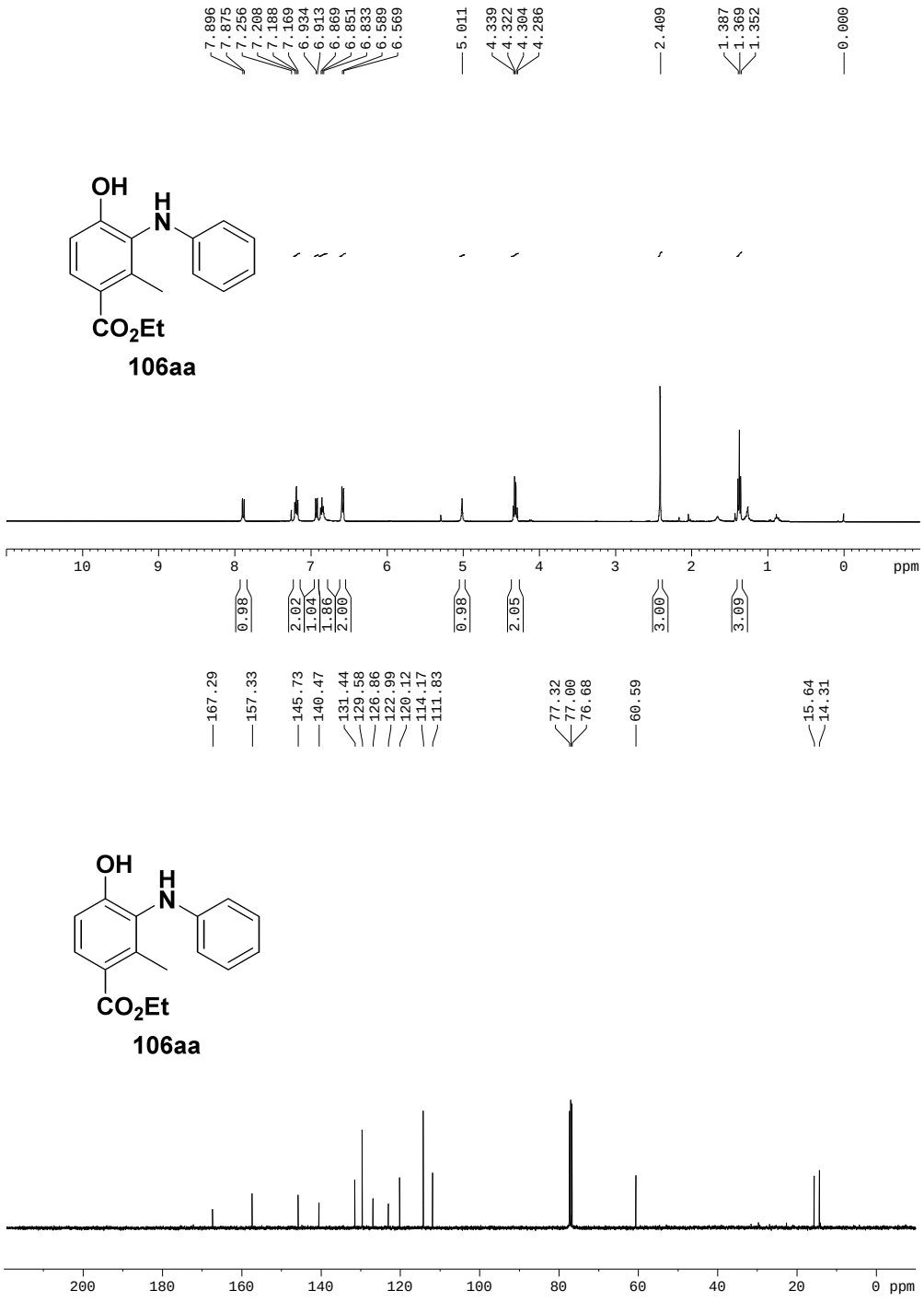


Figure-9: ^{1}H NMR and ^{13}C NMR Spectrum of product **106aa**

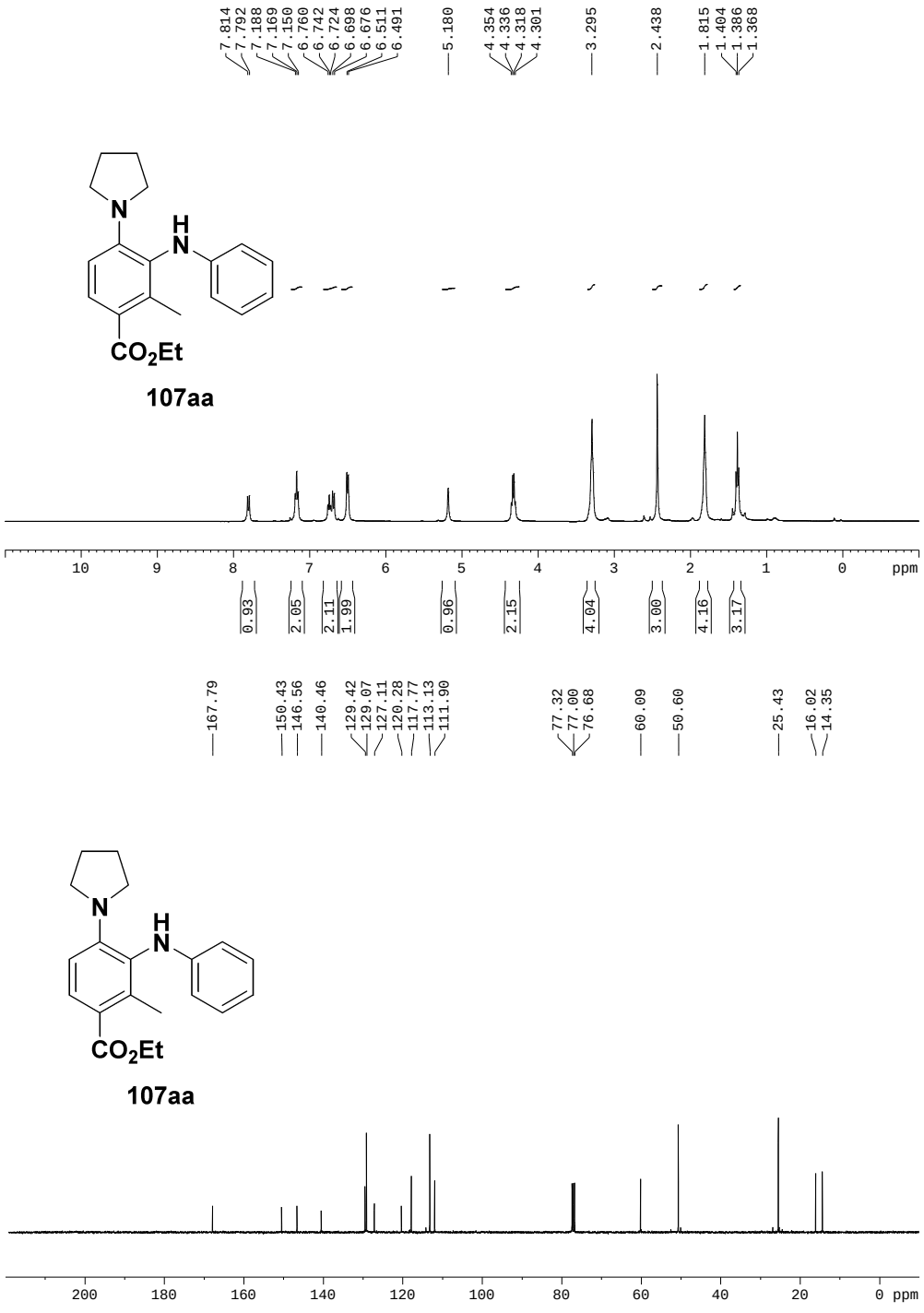
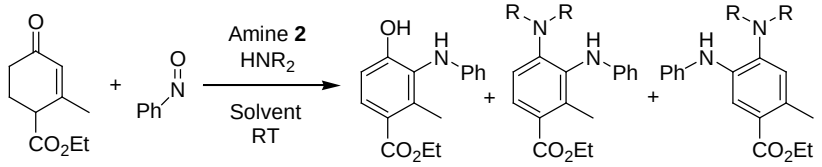


Figure-10: ^{1}H NMR and ^{13}C NMR Spectrum of product **107aa**

This is good demonstration for involvement of autocatalysis in present reactions (Table 11, entry 13). We envisioned the optimized condition to be 25 °C in DMSO under 5 mol% of pyrrolidine catalysis to furnish o-hydroxydiaryl-amine **106aa** in 85% yield (entry 9).

Table 12: Optimization of Direct Self-Catalyzed Cascade Synthesis of o-Aminediarylamines



88a **56a** **106aa** **107aa** **108aa**

entry	amine **2**	solvent (0.3 M)	H. ester **88a** (eq.)	time (h)	products yield (%)[a]		
					106aa	**107** & **108**	ratio **107/108**
1[b]	Pyrrolidine	DMSO	2.0	0.5	85	11	2:1
2[b]	Pyrrolidine	MeOH	2.0	1	35	45	1:1
3[b]	Pyrrolidine	EtOH	2.0	1	35	45	3:1
4[b]	Pyrrolidine	DCM	2.0	0.5	35	45	10:1
5[c]	Pyrrolidine	MeOH	1.0	1	10	80	10:1
6[c]	**Pyrrolidine**	**EtOH**	**1.0**	**1**	**10**	**80**	**10:1**
7[c]	Piperidine	EtOH	1.0	0.5	85	–	–
8[d]	**Pyrrolidine**	**EtOH**	**2.0**	**1**	**10**	**90**	**33:1**

[a] Yield refers to the column purified product. [b] All reactants pyrrolidine (0.3 mmol), nitrosobenzene **56a** (0.3 mmol) and Hagemann's ester **88a** (0.6 mmol) were mixed at the same time in solvent (0.3 M) and stirred at room temperature. [c] To the mixture of Hagemann's ester **88a** (0.3 mmol) and amine **2** (0.6 mmol) in solvent (0.5 mL), added the 0.5 mL solution of nitrosobenzene **56a** (0.3 mmol) over the period of 0.5 h and stirred at RT. [d] To the mixture of Hagemann's ester **88a** (0.6 mmol), pyrrolidine (0.3 mmol) and MS 4A (300 mg) in solvent (0.5 mL), added the 0.5 mL solution of nitrosobenzene **56a** (0.3 mmol) over the period of 0.5 h and stirred at RT.

In the investigation of EA/IA cascade reactions under pyrrolidine catalysis, product **106aa** was accompanied by interesting diamination products **107aa** and **108aa** with good conversion in EtOH via self-catalysis (Table 11, entry 12). To further exploit formation of this novel structures, we initiated our studies of the cascade EA/IA reaction by screening a number of known amines for the diamination of Hagemann's ester **88a** by 0.5 to 1.0 equivalents of both nitrosobenzene **56a** and amines **2** as shown in

Table 12. Proline, diamine and glycine as reagent in cascade reactions, didn't furnish the expected diamination products **107**/**108** in EtOH via self-catalysis and produced only amination product **106aa** (not shown in Table 12). Interestingly, pyrrolidine as reagent in self-catalyzed cascade reactions in DMSO furnished the amination product **106aa** as major product and diamination products **107**/**108** as minor (Table 12, entry 1). Same reaction in protic solvents furnished the amination product **106aa** and diamination **107aa**/**108aa** products with poor regioselectivity (entries 2 and 3). Slow addition of nitrosobenzene **56a** to Hagemann's ester **88a** under pyrrolidine self-catalysis in EtOH furnished the expected o-pyrrolidin-1-yl-diarylamines **107aa** and **108aa** in 80% yield with good selectivity (entry 6). We envisioned the optimized condition to be slow addition of **56a** to the mixture of **88a**, **2a** and MS 4A° at 25 °C in EtOH to furnish o-pyrrolidin-1-yl-diarylamines **107aa**/**108aa** in 90% yield with 33:1 regioselectivity (entry 8). A mechanistic aspect of this cascade EA/IA reaction is discussed in next section.

Hagemann's esters **88a-b, 88i-s** were prepared from alkyl acetoacetates and aldehydes with high yields in one-step according to literature procedures of Sangho Koo method[44a] and Bhaduri method[44b] with minor modifications as shown in Table A1. With an efficient organocatalytic cascade protocol in hand, the scope of the auto and self-catalyzed EA/IA cascade reactions was investigated with various Hagemann's esters **88a-s** and nitrosoarenes **56a-c**.[46] A series of 6-substituted Hagemann's esters **88a-s** were reacted with 0.5 equivalents of nitrosoarenes **56a-c** catalyzed by 5 mol% of pyrrolidine or piperidine at 25 °C in DMSO (Table 13). The o-hydroxy-diarylamines **106** were obtained as single isomers with excellent yields. The reaction of **88a** with 1-methyl-2-nitroso-benzene **56b** furnished the o-hydroxydiarylamine **106ab** as a single isomer, in good yield (Table 13). Synthesis of o-hydroxydiarylamine **106ac** from **88a**, **56c** and **2a** at 25 °C taken longer reaction time (12 h), but reaction at 65 °C furnished the product **106ac** with good yield within 2.5 h (Table 13). Both aliphatic and aromatic substituted Hagemann's esters **88i-r** were generated expected o-hydroxy-diarylamines **106** with nitrosoarenes **56a-c** in excellent yields (Table 13).

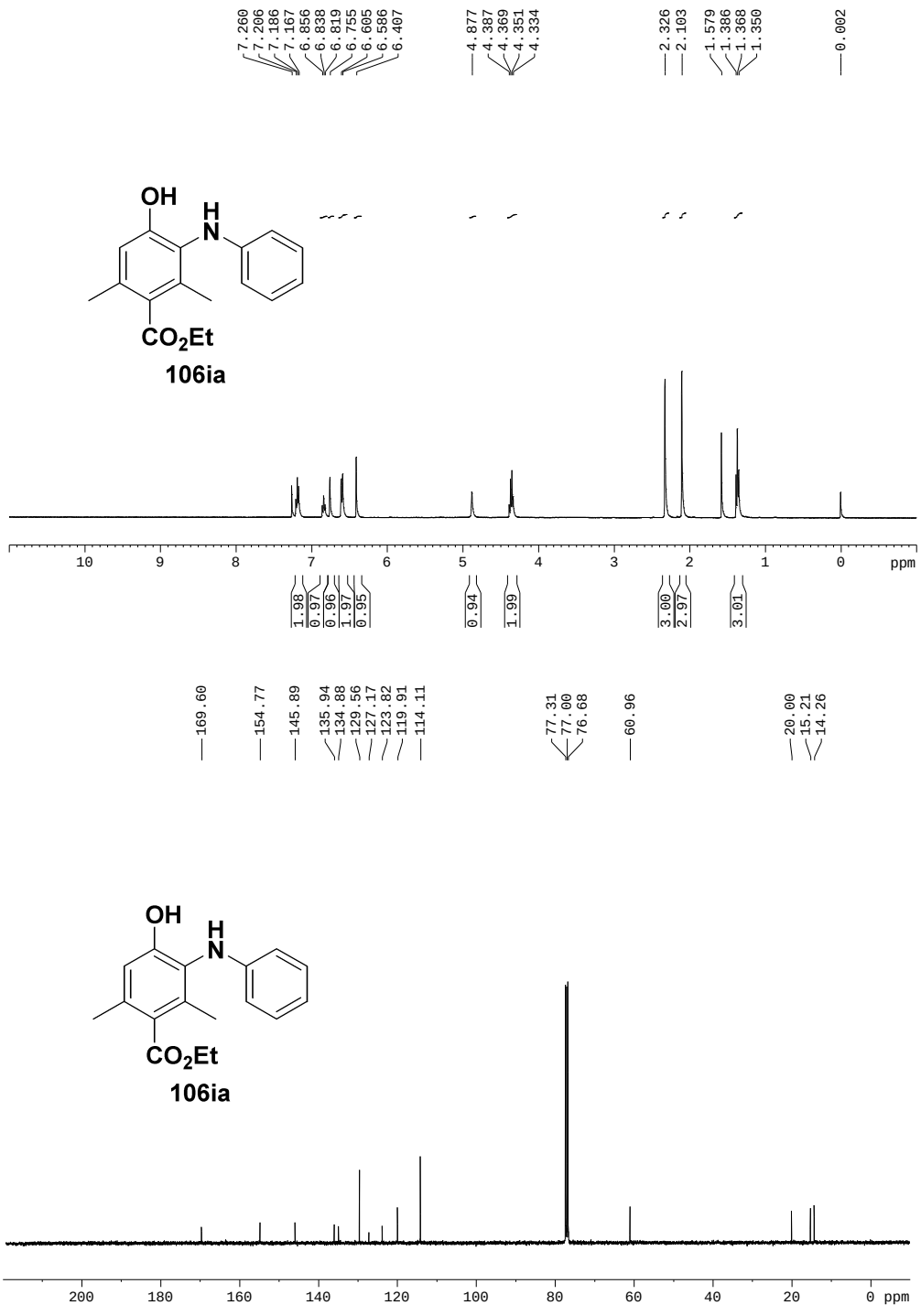


Figure-11: ^{1}H NMR and ^{13}C NMR Spectrum of product **106ia**.

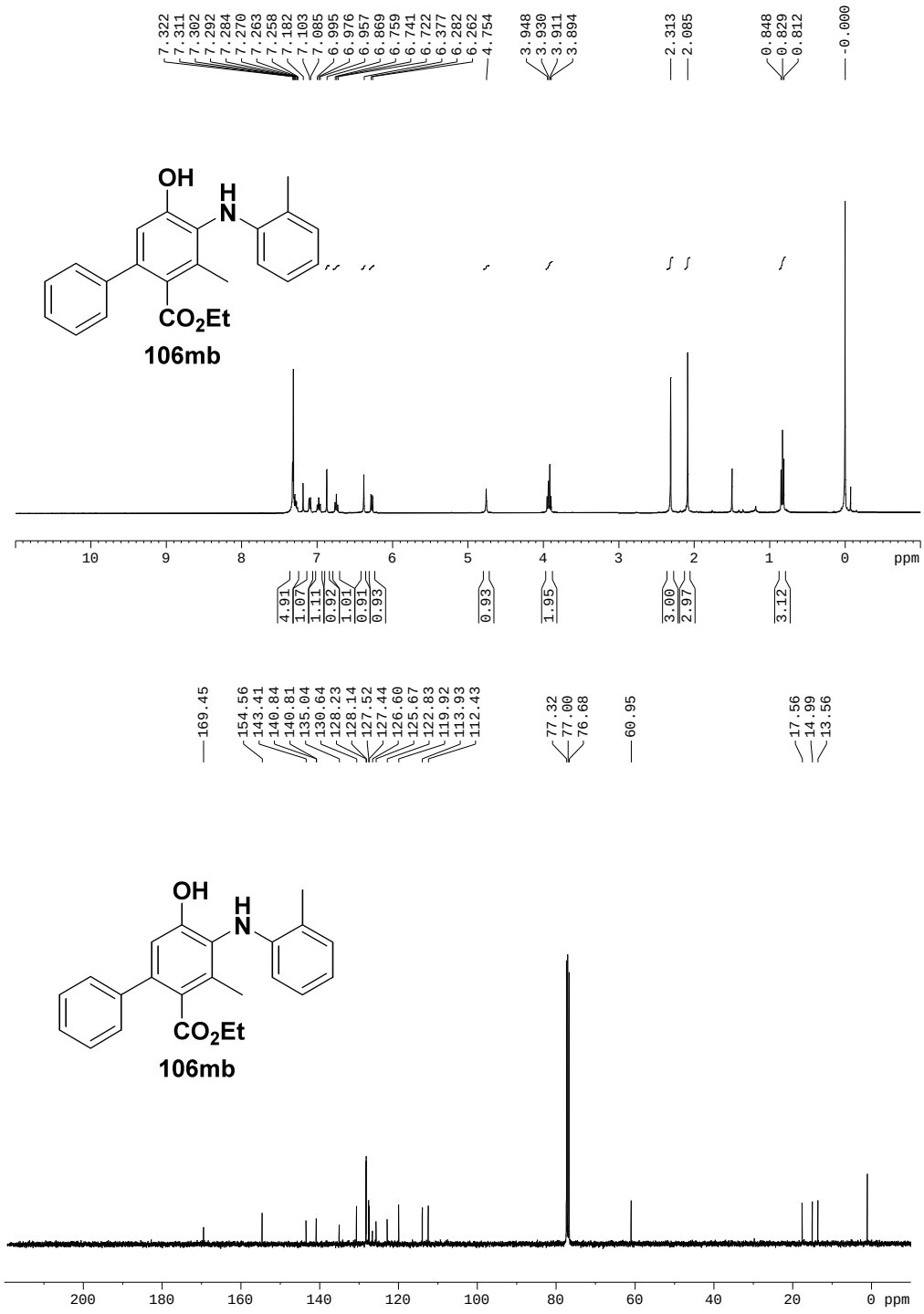
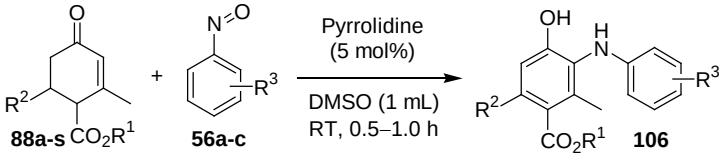
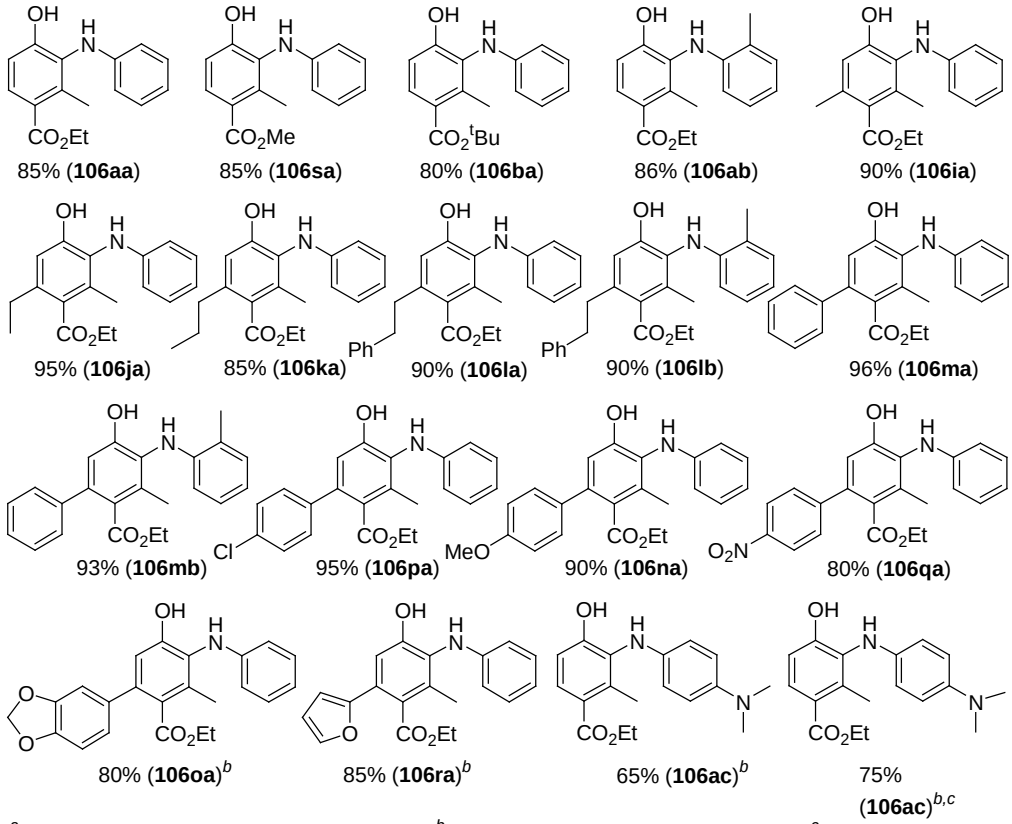


Figure-12: ^{1}H NMR and ^{13}C NMR Spectrum of product **106mb**.

Table 13: Chemically Diverse Libraries of o-Hydroxydiarylamines[a]



88a-s **56a-c** **106**

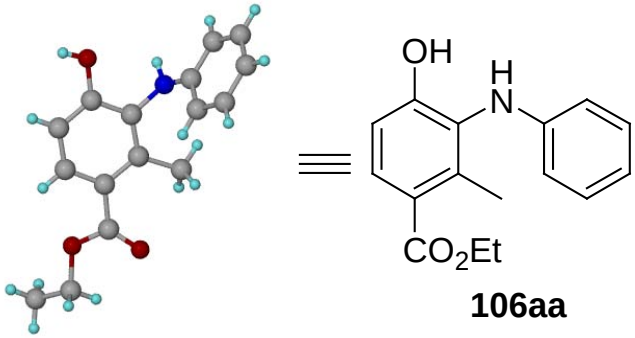


[a] Yield refers to the column purified product. [b] Piperidine (5 mol%) used as catalyst. [c] Reaction performed at 65 °C.

Rate of EA/IA cascade reactions are accelerated by in situ generated products **106** and these reactions are ideal examples for the bio-mimetic auto-catalysis of functionalized amines in organic reactions.[27b-c,47] Structure and regio-chemistry of o-hydroxy-diarylamines **106** were confirmed by ^{1}H NMR, ^{13}C NMR [for example see Fig. 9,11-12] and mass analysis and also finally conformed by X-ray structure analysis on **106aa** as shown in scheme 10.[48] With the success of cascade synthesis of highly functionalized o-hydroxy-diarylamines **106**, we continued our investigation for generation of highly

functionalized diversity oriented library of cascade o-pyrrolidin-1-yl-diarylamines **107** under self-catalysis.

Scheme 10: Crystal structure of 4-Hydroxy-2-methyl-3-phenylamino-benzoic acid ethyl ester (**106aa**)



106aa

The results in Table 14 demonstrate the broad scope of this novel green methodology covering a structurally diverse group of Hagemann's esters **88a-s**, pyrrolidine and nitrosobenzenes **56a-c**. Cascade EA/IA reaction of Hagemann's esters **88b** & **88s**, nitrosobenzene **56a** and pyrrolidine furnished the regioselective diamines **107ba** and **107sa** in 11:1 ratio with >85% yield (Table 14). Unexpectedly, cascade product **107ab** furnished with moderate yield in 3:1 isomeric ratio from **88a**, pyrrolidine and **56b**. 4-*N*,*N*-Dimethyl nitrosobenzene **56c** didn't furnished the expected cascade EA/IA product**107ac** at 25 °C, but given only <5% of expected **107ac** along with 40% of o-hydroxy-diarylamine **106ac** at 65 °C in EtOH, may be due to the electronic factor of NMe_2 group. Interestingly, all 6-substituted Hagemann's esters **88i-r** furnished expected o-pyrrolidin-1-yl-diarylamines **107ia-ra** with good yields as single isomer in self-catalyzed EA/IA cascade reactions as shown in Table 14. Structure and regiochemistry of o-pyrrolidin-1-yl-diarylamines **107** were confirmed by ^{1}H NMR, ^{13}C NMR [for example see Fig. 10,13-14] and mass analysis and also finally confirmed by X-ray structure analysis on **107pa** as shown in scheme 11.[49]

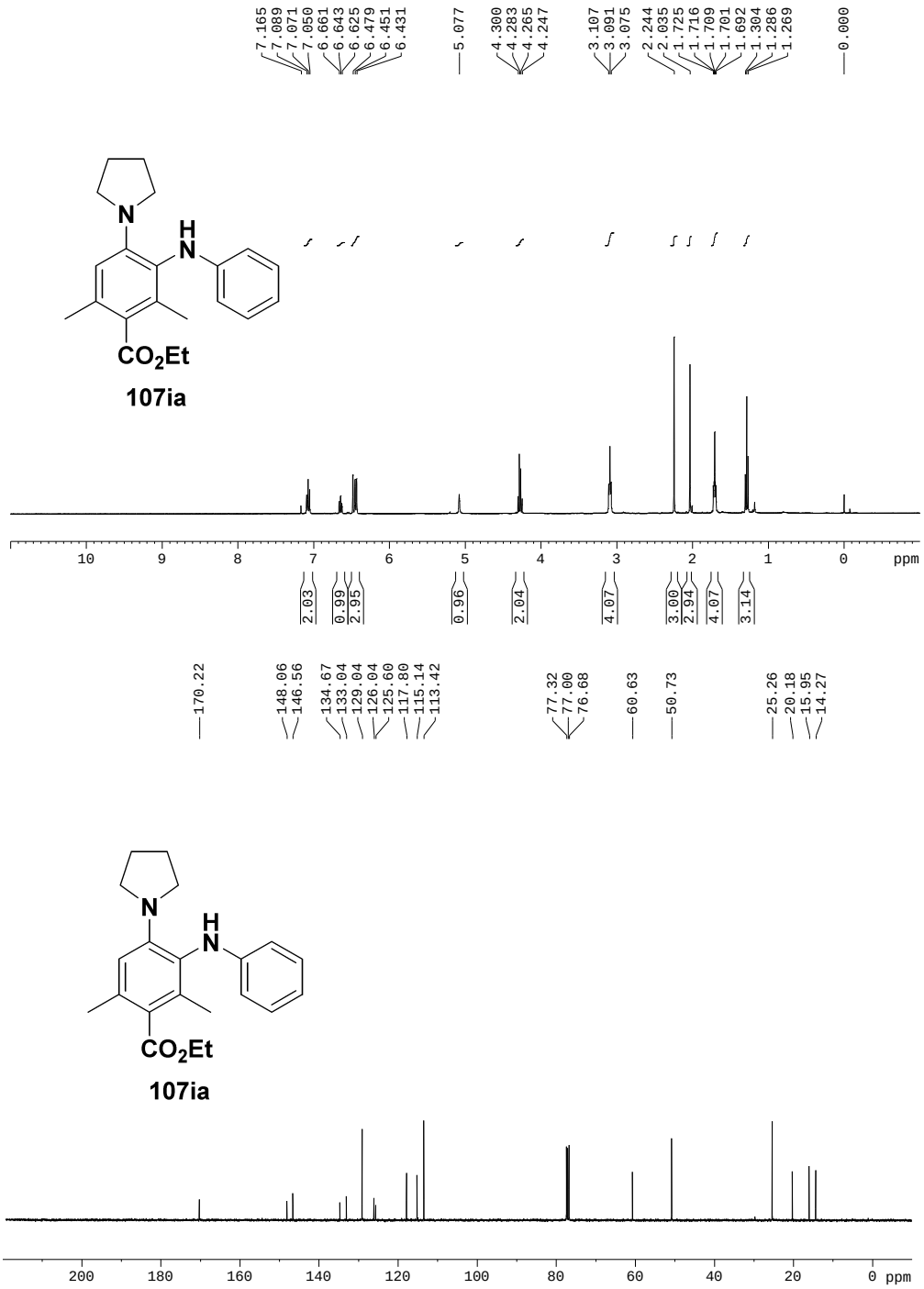


Figure-13: ^{1}H NMR and ^{13}C NMR Spectrum of product **107ia**

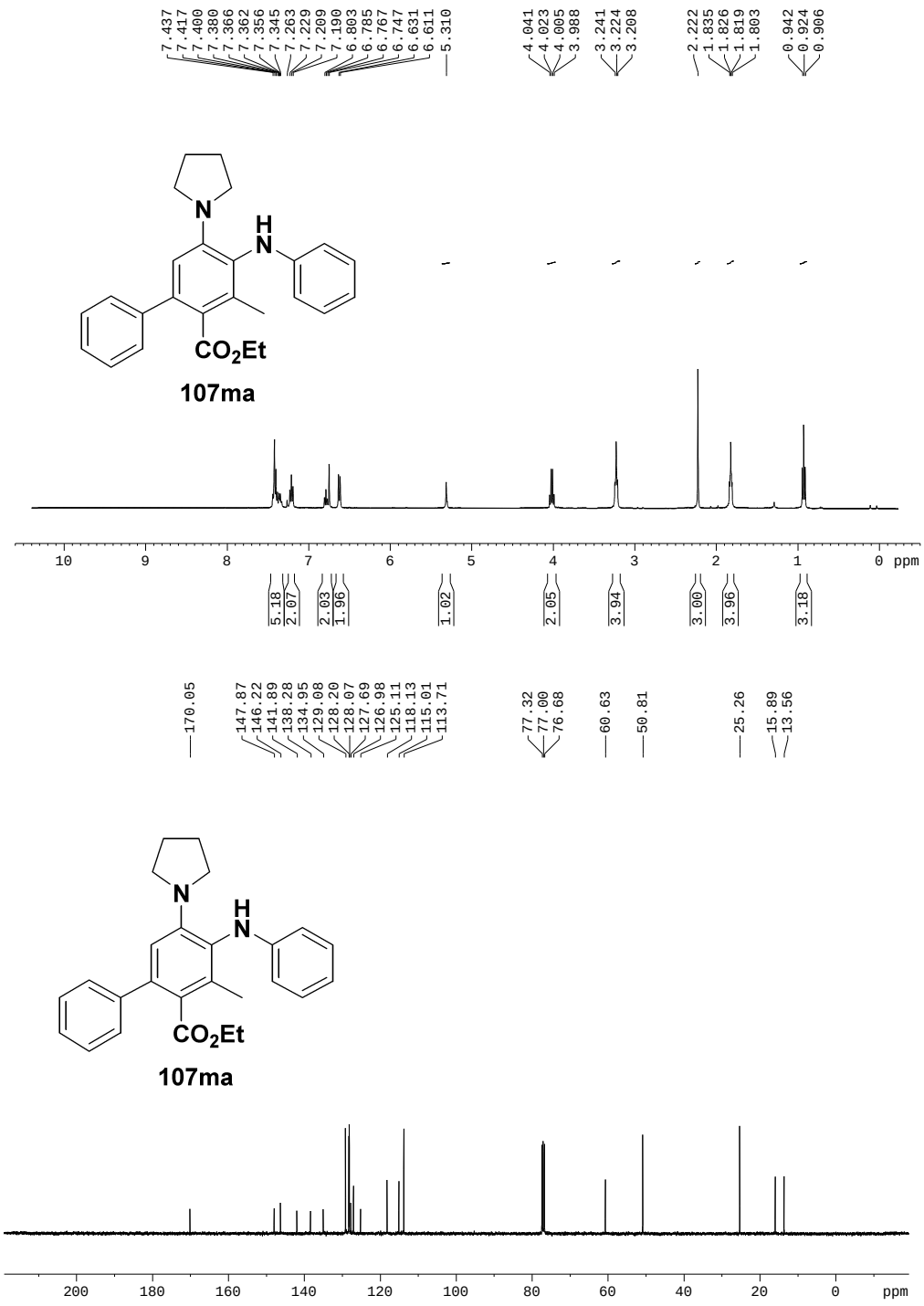
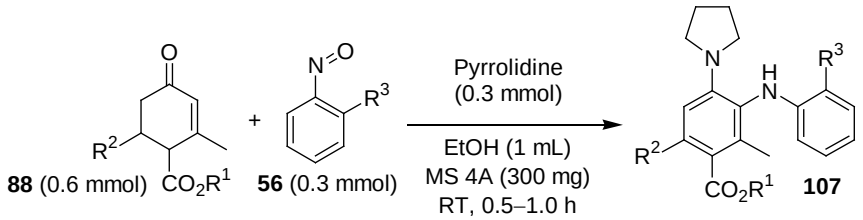
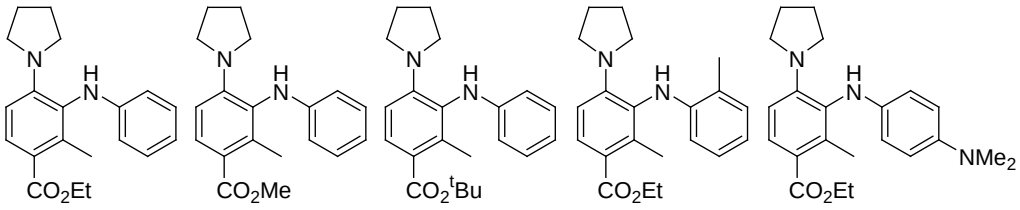


Figure-14: ^{1}H NMR and ^{13}C NMR Spectrum of product **107ma**.

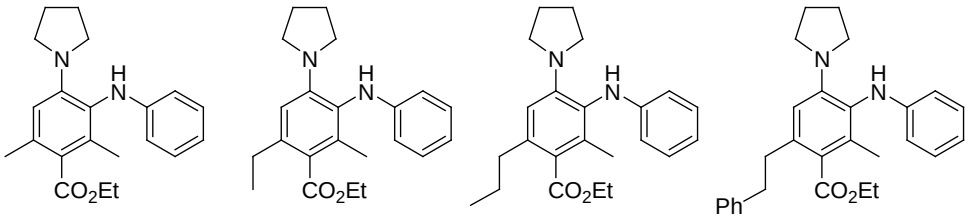
Table 14: Chemically Diverse Libraries of o-Pyrrolidin-1-yl-diarylamines[a]



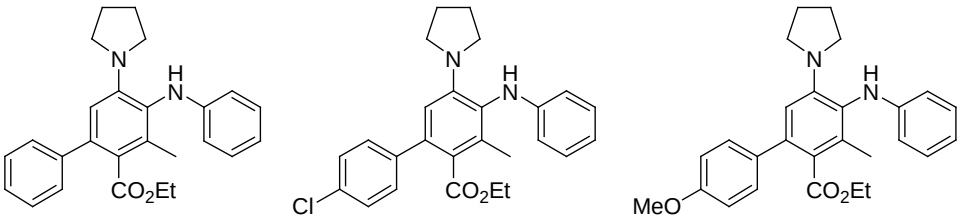
88 (0.6 mmol) **56** (0.3 mmol) **107**



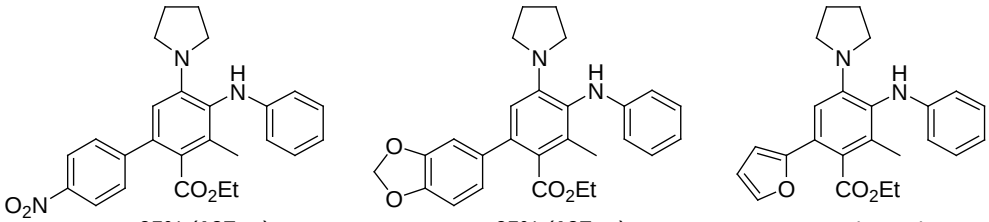
90% (**107aa**) 85% (**107sa**)[b] 88% (**107ba**)[b] 30% (**107ab**)[c] <5% (**107ac**)[d]



75% (**107ia**) 65% (**107ja**) 75% (**107ka**) 65% (**107la**)



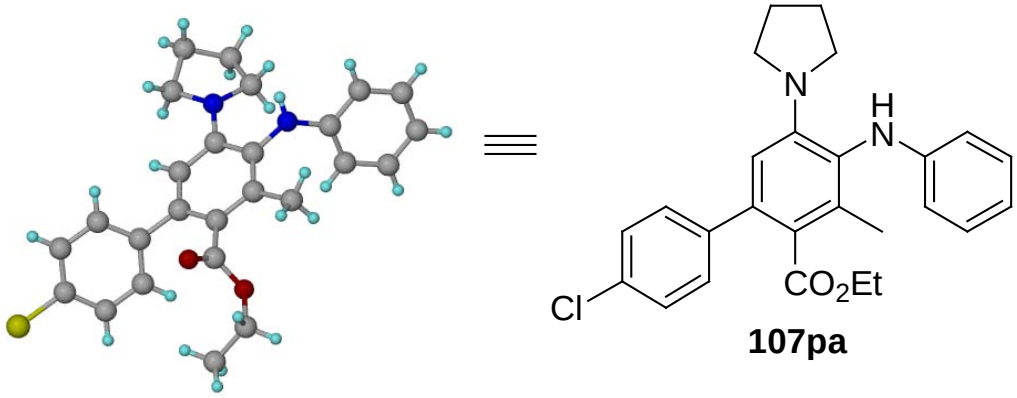
75% (**107ma**) 85% (**107pa**) 65% (**107na**)



65% (**107qa**) 65% (**107oa**) 55% (**107ra**)

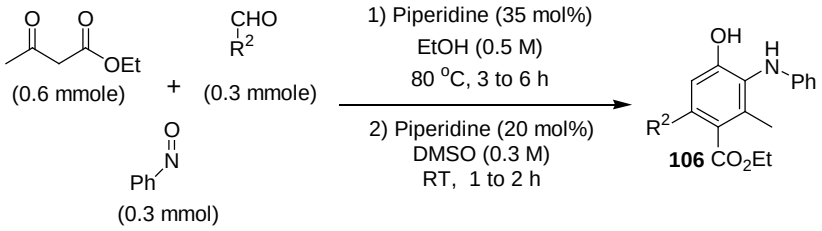
[a] In all reactions, 10-35% of corresponding substituted o-hydroxy-diarylamines **106** were isolated. Yield refers to the column purified product. [b] 11:1 ratio of regio-isomers **107/108** are isolated. [c] 3:1 ratio of **107/108** are isolated. [d] Reaction performed at 65 ^{o}C for 2.5 h and 40% of product **106ac** were isolated.

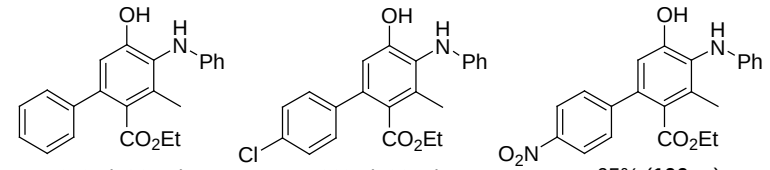
Scheme 11: 4'-Chloro-3-methyl-4-phenylamino-5-pyrrolidin-1-yl-biphenyl-2-carboxylic acid ethyl ester (**107pa**).



After successful demonstration of the piperidine-catalyzed cascade K/M/A/DC and EA/IA reactions, we decided to investigate the combination of these two cascade reactions in one-pot. Reaction of two equivalents of ethyl acetoacetate and benzaldehyde under piperidine-catalysis in EtOH at 80 °C for 3-6 h furnished the expected Hagemann's ester **88m**, which on treatment with nitrosobenzene **56a** at 25 °C in same solvent didn't furnished the expected o-hydroxydiarylamine **106ma** in good yield; but removing the solvent EtOH by vacuum pump and adding solvent DMSO, 20 mol% of piperidine and nitrosobenzene **56a** to the reaction mixture of cascade K/M/A/DC furnished the expected o-hydroxydiarylamine **106ma** in good yield as shown in Table 15. Successful combination of two cascade K/M/A/DC and EA/IA reactions under piperidine-catalysis was demonstrated by two more examples as shown in Table 15 and this one-pot synthetic strategy will show much impact on synthesis of functionalized small molecules.

Table 15: Combination of Cascade Knoevenagel/Michael/Aldol Condenasation/Decarboxylation and Cascade Enamine Amination/Iso-aromatization Reactions in One-Pot[a,b]

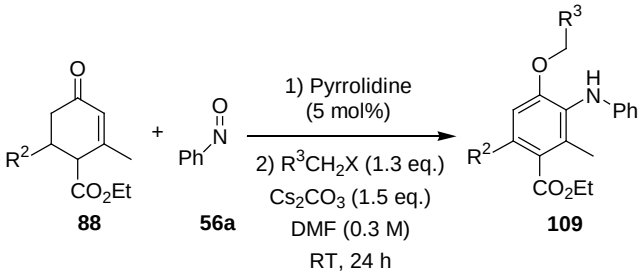


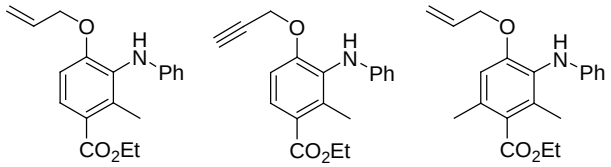


65% (**106ma**) 80% (**106pa**) 65% (**106qa**)

[a] See Experimental Section. [b] Yield refers to the column purified product.

Table 16: Amine-Cs_2CO_3-Catalyzed Enamine Amination/Iso-aromatization/Alkylation Reactions in One-Pot[a,b]





70% (**109aa**) 75% (**109ab**) 70% (**109ia**)

[a] See Experimental Section. [b] Yield refers to the column purified product.

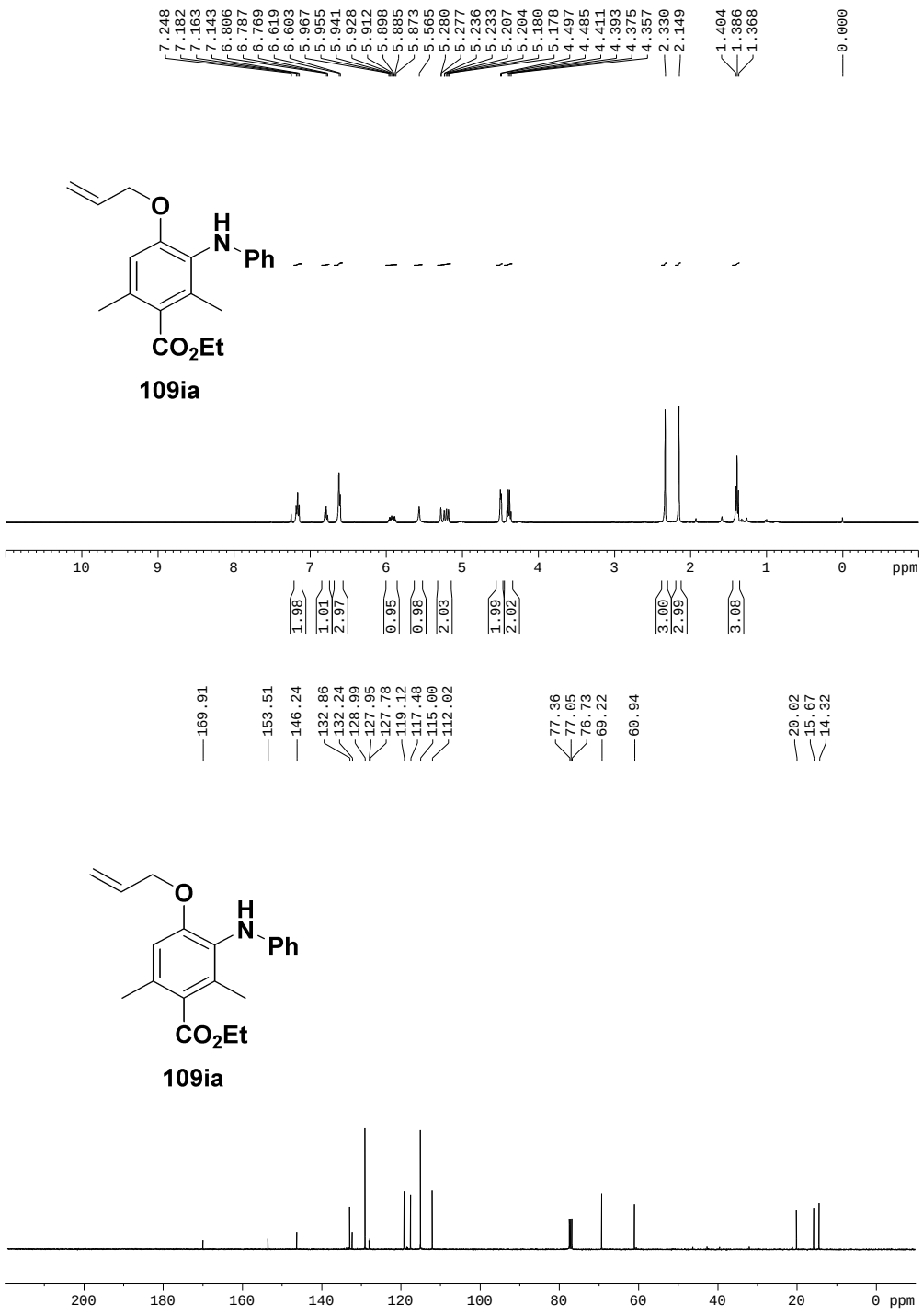
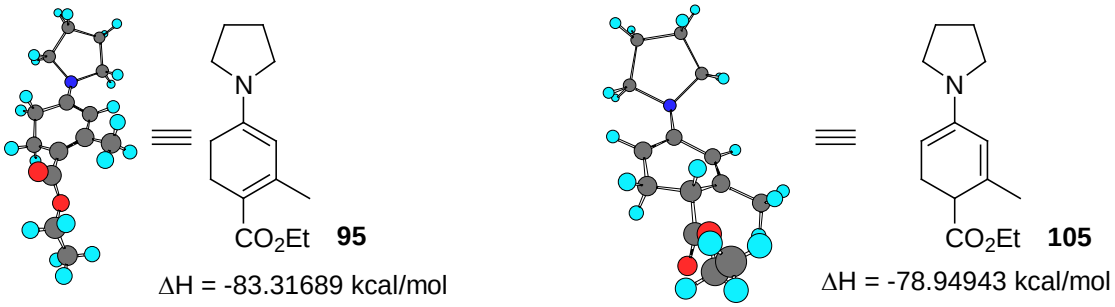


Figure-15: ^{1}H NMR and ^{13}C NMR Spectrum of product **109ia**.

With pharmaceutical applications in mind, we extended the two-component cascade EA/IA reactions into a novel amine/Cs_2CO_3-catalyzed three-component EA/IA/A reaction of **88a** and **88i**, **56a** with allyl and propargyl bromides in one-pot as shown in Table 16. o-Alkyloxy-diarylamines **109** were constructed in good yields with high selectivity as shown in Table 16. The products structures were confirmed by ^{1}H NMR, ^{13}C NMR [for example see Fig. 15] and mass analysis. This method will be showing much impact on synthesis of carbazole alkaloids.[41a]

The possible reaction mechanism for regioselective synthesis of cascade products **106** and **107** through reaction of Hagemann's ester **88a**, nitrosobenzene **56** and pyrrolidine **2a** is illustrated in Scheme 13. First, reaction of pyrrolidine **2a** with Hagemann's ester **88a** generates the imine cation **94aa**, which will transform into both dienamines **95** (thermodynamic stable product, major) and **105** (kinetic product, minor) based on reaction conditions. The energy difference (ΔH) between the two dienamines **95** and **105** is 4.698 kcal/mol based on AM1 and 4.367 kcal/mol based on PM3 calculations. Minimized structures of thermodynamic stable and kinetic stable enamines **95** and **105** based on MOPAC calculations are depicted in the Scheme 12.[50]

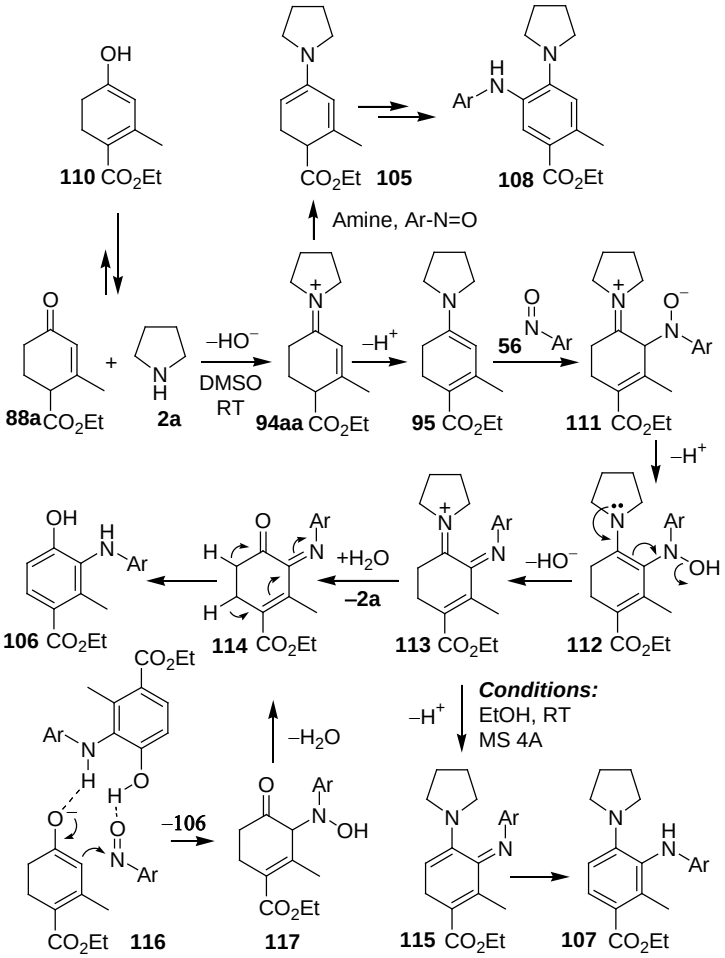
Scheme 12: Minimized structures of thermodynamic stable and kinetic stable enamines **95** and **105** based on MOPAC calculations



Since the difference in ΔH's between the two dienamines of **95** and **105** are >4 kcal/mol, formation of thermodynamic stable dienamine **95** will be major under mild

organocatalysis conditions. Slow addition of nitrosoarenes **56** to the reaction mixture of **88** and **2a** controlled the formation of kinetic dienamine **105**, may be due the basic nature of nitrosoarenes **56** and this was supported by results in Tables 12 and 14. Reaction of push-pull dienamine **95** with **56** furnish the selectively nitroso aldol product **112**, which will give imine product **113** by losing hydroxide ion. Hydrolysis followed by iso-aromatization of imine product **113** converted into highly substituted o-hydroxydiarylamine **106** under amine catalysis. Imine product **113** was transformed into highly substituted o-pyrrolidin-1-yl-diarylamines **107** via iso-aromatization under

Scheme 13: Proposed Reaction Mechanism



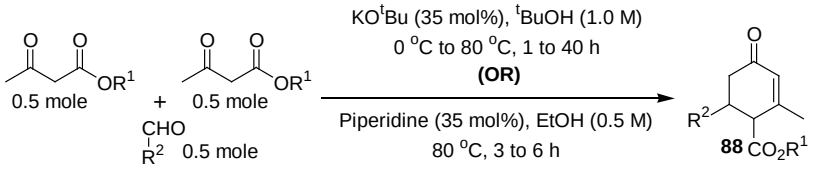
suitable conditions (EtOH and MS 4A°). Hydrolysis of imine **113** is more solvent dependent as shown in Tables 11 and 12, means this hydrolysis step fast in DMSO than in EtOH may be due to the more interactions with water. Similar manner, regio-isomer **108** also furnished from kinetic dienamine **105**. As we discussed in this chapter, these cascade reactions are auto-catalyzed and product **106** can catalyze the nitroso aldol reaction of enolate **110** of **88a** with **56** to form **117** via hydrogen bonding transition state **116**, which will transform into expected product **106** through imine **114** as shown in Scheme 13 (see Table 11, entries 13 and 14).

4.3 CONCLUSION

In this chapter, we have described the metal-free synthesis of highly substituted anilines **106**, **107** and **109** from simple starting materials via cascade EA/IA and K/M/A/DC/EA/IA and EA/IA/A reactions under amine catalysis. The cascade reaction proceeds in good yields with high selectivity using pyrrolidine or piperidine as the catalyst. Furthermore, we have demonstrated the bio-mimetic auto and self-catalysis in amine-catalyzed cascade reactions.

ANNEXURE-I: DIRECT ORGANO- OR KO^{t}BU-CATALYZED CASCADE SYNTHESIS OF HAGEMANN'S ESTERS.

Table A1: Direct Organo- and KO^{t}Bu-Catalyzed Cascade Synthesis of Chemically Diverse Libraries of Hagemann's esters **88**.



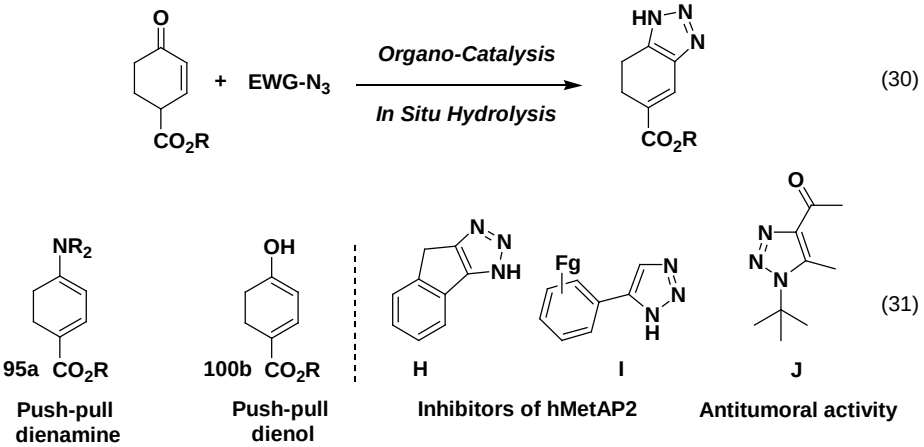
entry	R^1/R^2	product	yield (%)[a,b]	entry	R^1/R^2	product	yield (%)[a,b]
1	C_2H_5/H	**88a**	90	8	C_2H_5/C_6H_5	**88m** (3.0:1)	(90)[b]
2	CH_3/H	**88s**	75	9	C_2H_5/C_6H_5	**88m** (3.4:1)	50
3	^{t}Bu/H	**88b**	50	10	C_2H_5/4-ClC_6H_4	**88p** (4.8:1)	55 (80)
4	C_2H_5/CH_3	**88i** (2:1)	80	11	C_2H_5/4-$OMeC_6H_4$	**88n** (1.6:1)	60 (50)
5	C_2H_5/C_2H_5	**88j** (1.6:1)	65 (60)	12	C_2H_5/4-$NO_2C_6H_4$	**88q** (2.4:1)	50 (85)
6	C_2H_5/C_3H_7	**88k** (1.7:1)	90	13	C_2H_5/3,4-$(OCH_2O)C_6H_3$	**88o** (2.8:1)	50 (70)
7	C_2H_5/PhC_2H_4	**88l** (1.6:1)	90	14	C_2H_5/C_4H_3O	**88r** (3.4:1)	70 (70)

[a] Yield refers to the column purified product. [b] Yield in parentheses obtained from piperidine (35 mol%) catalysis.

5. AMINO ACID-CATALYZED CASCADE [3+2]-CYCLOADDITION/HYDROLYSIS REACTIONS BASED ON THE PUSH-PULL DIENAMINE PLATFORM: SYNTHESIS OF HIGHLY FUNCTIONALIZED *NH*-1,2,3-TRIAZOLES

5.1 INTRODUCTION

1,2,3-Triazoles are an important class of heterocycles, which display very large spectrum of biological activities and are widely used as pharmaceuticals and agrochemicals.[51] Also compounds containing 1,2,3-triazoles have found industrial applications as corrosion inhibitors, lubricants, dyes, and photostabilizers.[51] As such, the development of new and more general methods for their preparation is of significant interest.[52] The conventional method to triazoles is the Huisgen 1,3-dipolar cycloaddition of alkynes with azides. Recent discovery of the novel technology of Cu^{I}-catalyzed [3+2]-cycloaddition reactions of terminal alkynes with organic azides to provide a general route to a variety of 1,4-disubstituted 1,2,3-triazoles in good yields, and it has become a paradigm of a "click chemistry" reaction.[53] The advent of click reaction technology triggered a burst of activity in the synthesis of a huge variety of differently substituted 1,2,3-triazoles as *in vitro* and *in vivo* conditions.[54]



Recently, the copper-catalyzed azide-alkyne click reaction has proven extremely valuable for attaching small molecular probes to various biomolecules in a test tube or on fixed cells.[55] However, its use for biomolecule labeling in live cells or organisms is prohibited by the requirement of a cytotoxic copper catalyst.[55]

As part of our program to engineer direct organocatalytic cascade reactions,[14b,27a-f,27h,56] herein we have discovered a copper-free, novel and green technology for the synthesis of highly substituted α-diazo compounds and *N*H-1,2,3-triazoles using organocatalytic cascade enamine amination/elimination (EA/E) and [3+2]-cycloaddition/hydrolysis ([3+2]-CA/H) reactions from commercially available activated enones, azides and amines/amino acid (eq. 30). In this chapter, first time we discovered the organocatalytic approach to the synthesis of *N*H-1,2,3-triazole products.

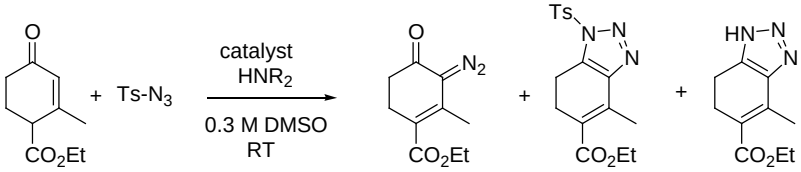
Over the last few years, we have been interested in amine mediated in situ generation and application of novel push-pull dienamines/push-pull dienols (**A** and **B**, see eq. 31) in cascade reactions from Hagemann's esters with nitrogenated species for the formation of C-N bonds.[1a-c,57] During our investigation for new coupling species for such processes, we decided to explore the potential ability of the organic azides to participate in an amine/amino acid-catalyzed coupling reaction. We expected that the coupling of an organic azide with in situ generated push-pull dienamines would lead to protected 1,2,3-triazoles. However, protected 1,2,3-triazoles were not detected and instead *N*H-1,2,3-triazoles were obtained under the standard reaction conditions. This unexpected cascade result represents a novel methodology for the preparation of *N*H-1,2,3-triazoles and a new reactivity for amino acid catalysts. Herein, we report our findings regarding these new amino acid-catalyzed cascade reactions.

5.2 RESULTS AND DISCUSSION

We initiated our preliminary studies of the cascade EA/E or [3+2]-CA/H reactions by screening a number of known and novel organocatalysts for the amination of

Hagemann's ester **88a** by 0.5 to 1.0 equivalents of *p*-toluenesulfonyl azide (TsN_3) **118a** and some representative results are shown in Table 17. Interestingly, reaction of **88a** with 1.0 equiv of TsN_3 **118a** in DMSO under 20-mol% of glycine **14d**-catalysis furnished the cascade [3+2]-CA/H product *N*H-1,2,3-triazole **121aa** as single product with only 25% yield (Table 17, entry 1). Same reaction under 20-mol% of L-Proline **14a**-catalysis also furnished the *N*H-1,2,3-triazole **121aa** as single product with 55% yield (Table 17, entry 2). Interestingly, reaction of **88a** with 1.0 equiv of **118a** under

Table 17: Preliminary study for the reaction optimisation.[a]



88a **118a** **119aa** **120aa** **121aa**

Entry	Catalyst [20 mol%]	*t*[h]	Yield[%][b]		
			119aa	**120aa**	**121aa**
1	glycine (**14d**)	96	–	–	25
2	proline (**14a**)	24	–	–	55
3	diamine (**2i**)[c]	0.75	83	–	–
4	piperidine (**2b**)	0.75	83	–	–
5	morpholine (**2c**)	0.75	73	–	–
6	pyrrolidine (**2a**)	1.0	67	–	–
7	benzylamine (**2d**)	0.75	83	–	–
8[d]	**2d**	0.75	85	–	–
9[e]	**2d**	0.70	90	–	–
10[f]	**2d**	0.75	80	–	–
11[g]	**2d**	0.75	70	–	–
12[h]	**2d**	0.75	80	–	–
13	Et_3N (**2g**)	1.5	65	–	–
14	$Me_2NCH_2CH_2OH$ (**2k**)	1.5	71	–	–
15	DBU (**2h**)	1.5	58	–	–
16	DABCO (**2l**)	1.5	77	–	–
17	DMAP (**2f**)	1.5	67	–	–

[a] Reactions were carried out in solvent (0.3 M) with 1.0 equiv. of **88a** relative to the **118a** in the presence of 20 mol% of catalyst . Ts = *p*-toluenesulfonyl; [b] Yield refers to the column-purified product. [c] (*S*)-1-(2-Pyrrolidinyl methyl)pyrrolidine (**2i**). [d] 30 mol% of **2d** was used. [e] 40 mol% of **2d** was used. [f] 2.0 equiv. of **88a** was used. [g] DMF used as solvent. [h] NMP used as solvent.

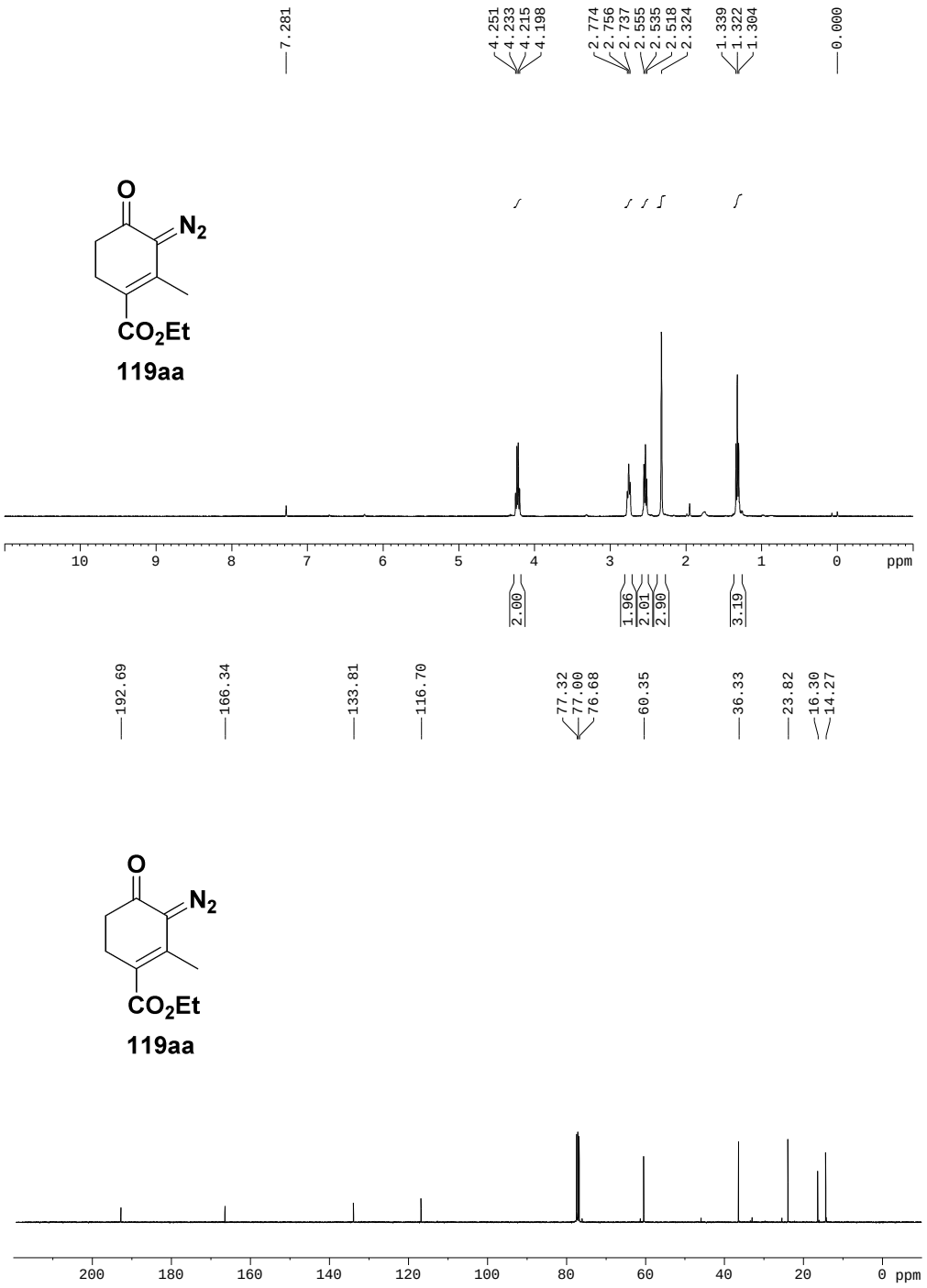


Figure-16: ^{1}H NMR and ^{13}C NMR Spectrum of product **119aa**.

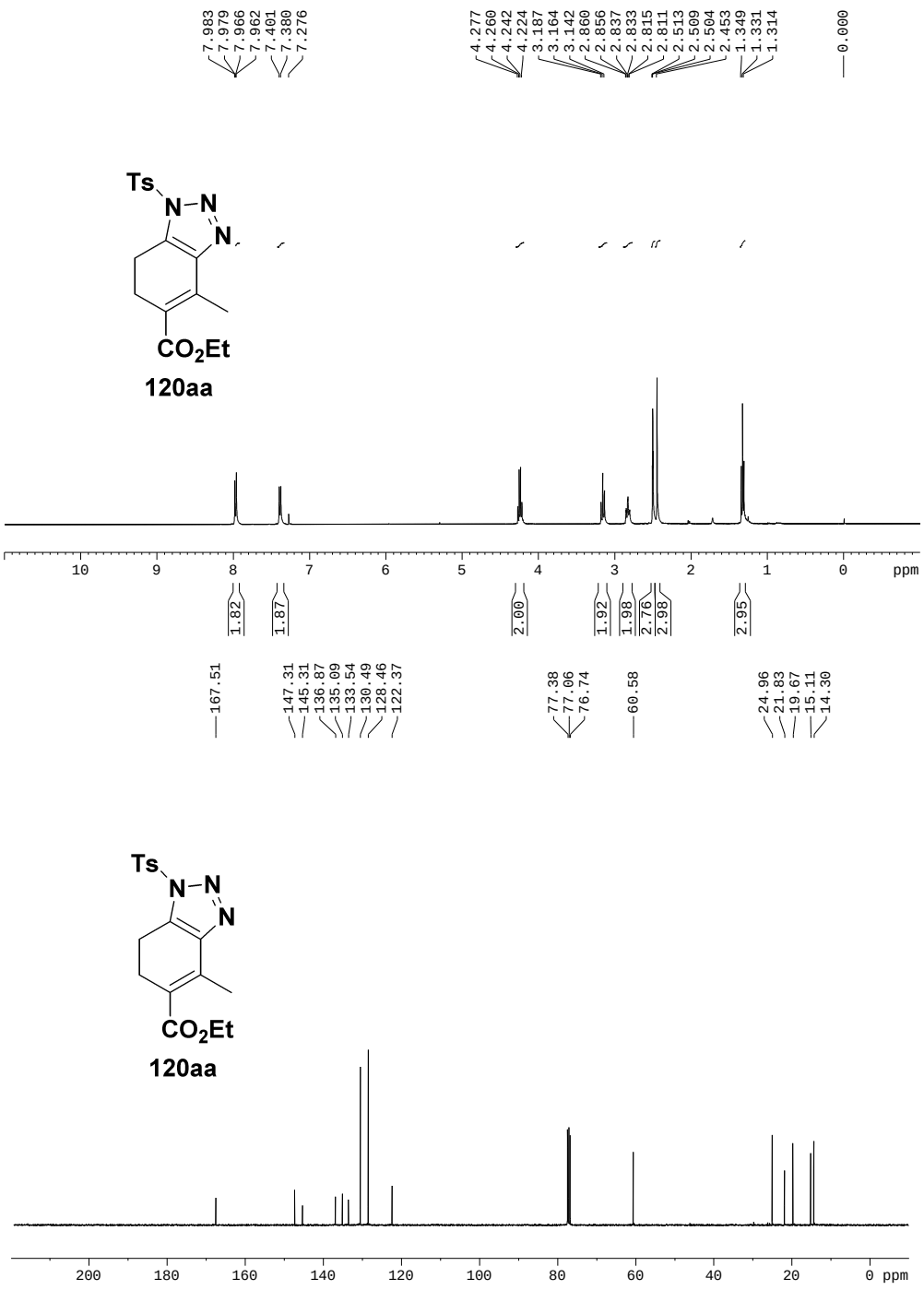


Figure-17: ^{1}H NMR and ^{13}C NMR Spectrum of product **120aa**.

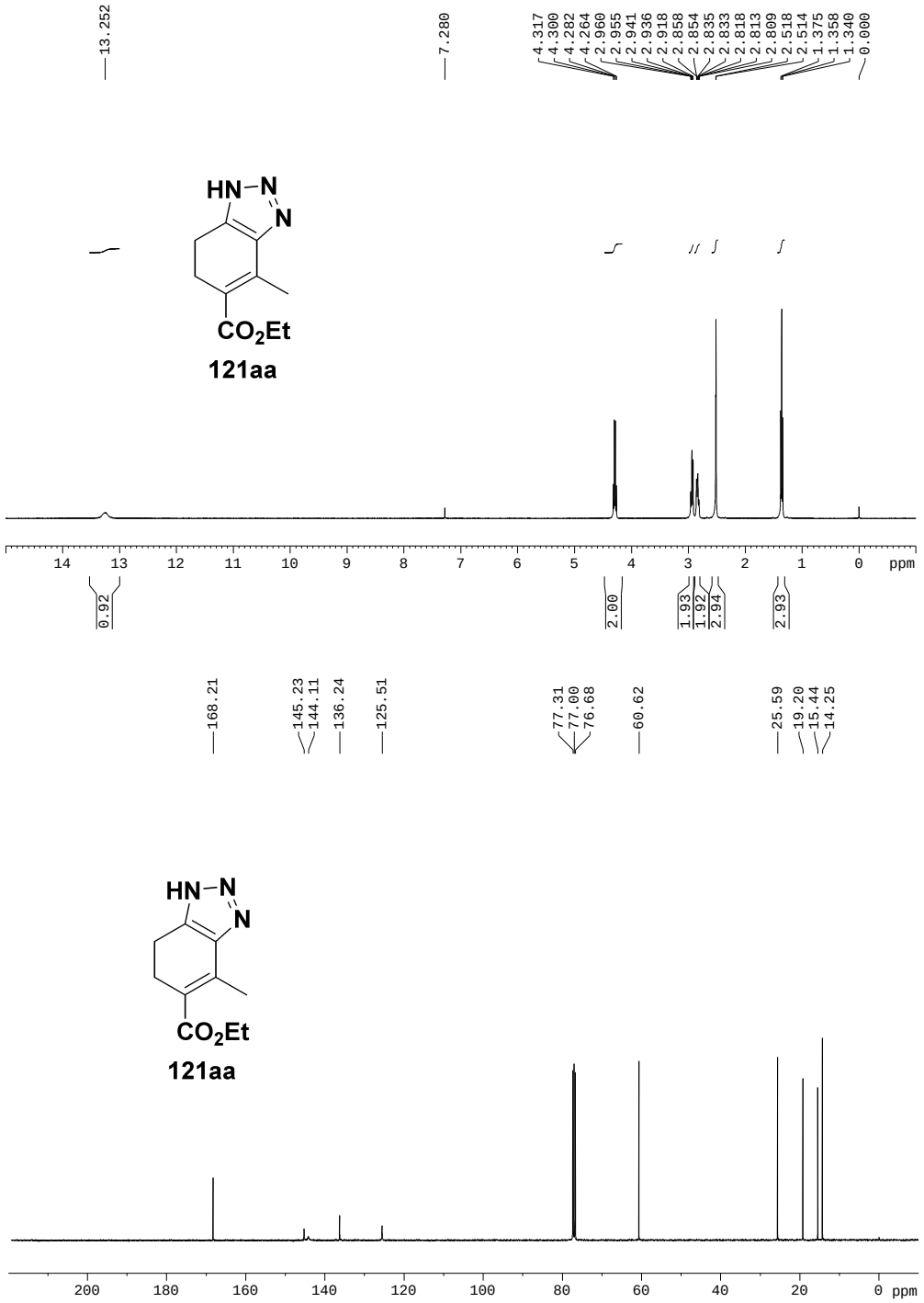
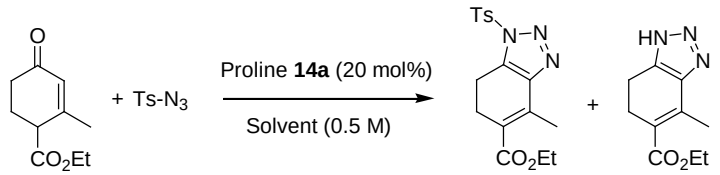


Figure-18: ^{1}H NMR and ^{13}C NMR Spectrum of product **121aa**.

diamine **2i**-catalysis generated the cascade EA/E diazo-product **119aa** with 83% yield in DMSO and there are no products from the cascade [3+2]-CA/H sequence (Table 17, entry 3). Secondary-amines like piperidine **2b**, morpholine **2c** and pyrrolidine **2a** catalysts also furnished the cascade EA/E diazo-product **119aa** with good yields in DMSO solvent (entries 4, 5 and 6). Primary amine, benzylamine **2d** also catalyzed the formation of cascade diazo-product **119aa** in very good yield (entries 7-9). Benzylamine-catalyzed cascade EA/E reactions are solvent dependent reactions, working well in aprotic polar solvents like DMSO, DMF and NMP but only <15% conversion is observed in other solvents like EtOH, CH_3CN, $CHCl_3$, THF, H_2O and [bmim]BF_4 (Table 17, entries 11-12). Addition of 20-mol % of simple tertiary-amines such as Et_3N **2g**, $Me_2NCH_2CH_2OH$ **2k**, DBU **2h**, DABCO **2l** and DMAP **2f** as catalyst in DMSO at 25 °C for 1.5 h furnished the cascade EA/E diazo-product **119aa** as single compound in 65–77% yields as shown in Table 17, entries 13–17. We envisioned the optimized condition to be 25 °C in DMSO under 20-40 mol% benzylamine **2d** catalysis to furnish the highly substituted diazo-product **119aa** in 83-90% yield (Table 17, entries 7-9).

Reaction of **88a** with **118a** under amino acid **14a**-catalysis furnished the interesting [3+2]-CA/H cascade product **121aa** as single product (Table 17, entry 2). Further to improve the reaction yield, we initiated our studies of the cascade [3+2]-CA/H reaction by screening a number of reaction conditions for the coupling of Hagemann's ester **88a** by 0.5 to 1.0 equiv. of TsN_3 **118a** under amino acid **14a**-catalysis, and some representative results are shown in Table 18. Reaction of **88a** with 1.0 equiv. of TsN_3 **118a** in EtOH under 20-mol% of proline **14a**-catalysis furnished the cascade [3+2]-CA/H product *N*H-1,2,3-triazole **121aa** as single product with only 30% yield (Table 18, entry 1). Interestingly, same reaction in MeOH furnished the unhydrolyzed 1,2,3-triazole **120aa** as single product with 35% yield (Table 18, entry 2). Reaction of **88a** with 1.0 equiv. of **118a** under **14a**-catalysis in DMSO at 70 °C for 5 h furnished the cascade [3+2]-CA/H product **121aa** in 65% yield (Table 18, entry 4).

Table 18: Reaction optimisation for the *N*H-1,2,3-triazole synthesis.



88a **118a** **120aa** **121aa**

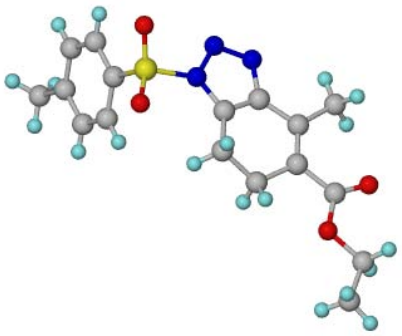
Entry	Solvent [0.5 M]	H. ester **88a** [eq.]	Temp [°C]	Time [h]	Products yield [%][a] **120aa**	**121aa**
1	EtOH	1.0	25	120	–	30
2	MeOH	1.0	25	120	35	–
3	DMSO	1.0	25	24	–	55
4	DMSO	1.0	70	5	–	65
5[b]	DMSO	1.0	25	24	–	76
6[c]	**DMSO**	**1.0**	**25**	**24**	**–**	**90**
7	DMF	1.0	25	24	55	10
8	NMP	1.0	25	24	60	10
9	**NMP**	**2.0**	**25**	**19**	**70**	**10**
10	**DMSO**	**2.0**	**25**	**24**	**–**	**94**
11	**DMSO**	**2.0**	**80**	**5**	**–**	**91**
12	DMSO	0.5	80	5	–	75

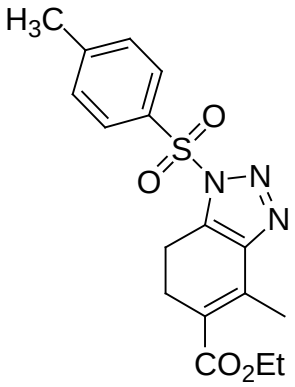
[a] Yield refers to the column purified product. [b] 40 mol% of proline were used. [c] 50 mol% of proline were used.

Increasing the catalyst **14a** loading from 20-mol% to 50-mol% or substrate **88a** loading from 1.0 equiv. to 2.0 equiv. yield of cascade product **121aa** increased drastically from 55% to 90/94% at 25 °C for 24 h in DMSO solvent as shown in Table 18, entries 5-6 and 10-11. Interestingly, amino acid-catalyzed cascade [3+2]-CA/H reactions are also solvent dependent reactions, working well in aprotic polar solvents like DMSO, DMF and NMP but only <15% conversion is observed in other solvents like CH_3CN, $CHCl_3$, THF, H_2O and *c*-C_6H_{12} (Results not presented in table 18). Cascade reaction of **88a** with **118a** under **14a**-catalysis in DMF at 25 °C for 24 h furnished the unhydrolyzed 1,2,3-triazole **120aa** in 55% yield accompanying with

product **121aa** in 10% yield as shown in Table 18, entry 7. Same cascade reaction in NMP as solvent furnished the products **120aa** and **121aa** in 60% and 10% yields respectively (Table 18, entry 8). We envisioned the optimized conditions to be addition of 2.0 equiv. of **88a** to TsN_3 **118a** under 20-mol% proline **14a**-catalysis in DMSO or NMP at 25 °C for 24 h to furnish the cascade products **121aa** and **120aa** in 94% and 70% yields respectively (Table 18, entry 9 and 10). The products structures were confirmed by ^{1}H and ^{13}C NMR [for example see Fig. 16-18], mass analysis and structure and regiochemistry of 4-methyl-1-(toluene-4-sulfonyl)-6,7-dihydro-*1H*-benzotriazole-5-carboxylic acid ethyl ester **120aa** and 4-methyl-6,7-dihydro-*1H*-benzotriazole-5-carboxylic acid ethyl ester **121aa** was finally confirmed by X-ray structure analysis as shown in Scheme 14 and Scheme 15[58,59]

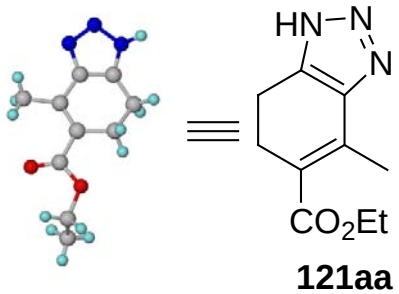
Scheme 14: Crystal structure of 4-methyl-1-(toluene-4-sulfonyl)-6,7-dihydro-1H-benzotriazole-5-carboxylic acid ethyl ester (**120aa**).





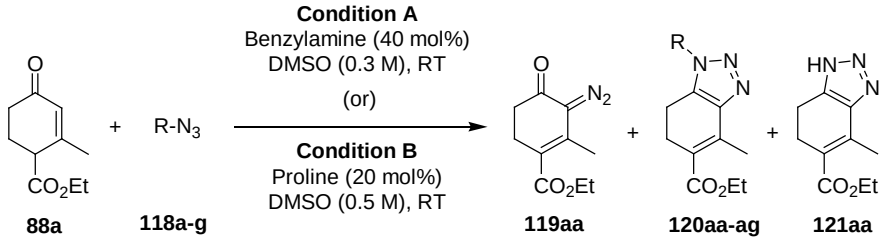
120aa

Scheme 15: Crystal structure of 4-methyl-6,7-dihydro-1H-benzotriazole-5-carboxylic acid ethyl ester (**121aa**).



121aa

Table 19: Effect of an azides **118a-g** on the cascade EA/E and [3+2]-CA/H reactions.[a]



88a **118a-g** **119aa** **120aa-ag** **121aa**

	Condition A			**Condition B**			
Entry	$R\text{-}N_3$ [1.0 equiv.]	Time [h]	Yield [%][b] **119aa**	$R\text{-}N_3$ [0.5 equiv.]	Time [h]	Products yield [%][b] **120aa-ag**	**121aa**
1	$4\text{-}CH_3C_6H_4SO_2N_3$ **118a**	0.75	90	$4\text{-}CH_3C_6H_4SO_2N_3$ **118a**	24	–	94
2	$CH_3SO_2N_3$ **118b**	0.75	84	$CH_3SO_2N_3$ **118b**	12	–	78
3	$C_2H_5OCON_3$ **118c**	72	–	$C_2H_5OCON_3$ **118c**	48	–	30
4	$4\text{-}NO_2C_6H_4SO_2N_3$ **118d**	26	20	$4\text{-}NO_2C_6H_4SO_2N_3$ **118d**	48	–	30
5	$2\text{-}NO_2C_6H_4SO_2N_3$ **118e**	12	20	$2\text{-}NO_2C_6H_4SO_2N_3$ **118e**	48	–	30
6	$C_6H_5CH_2N_3$ **118f**	48	–	$C_6H_5CH_2N_3$ **118f**	48	–	–
7	$(CH_3)_3SiN_3$ **118g**	72	–	$(CH_3)_3SiN_3$ **118g**	48	–	–

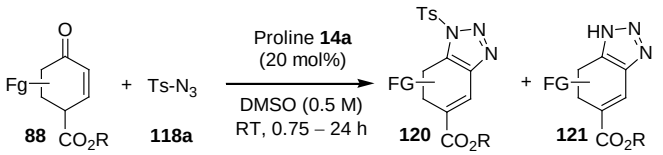
[a] See Experimental section. [b] Yield refers to the column-purified product.

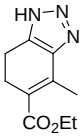
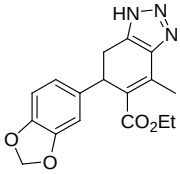
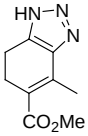
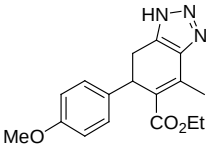
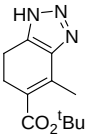
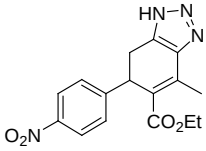
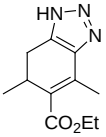
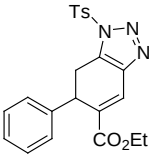
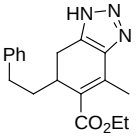
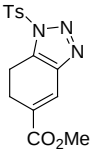
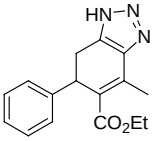
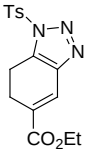
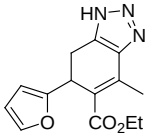
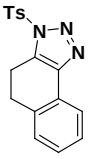
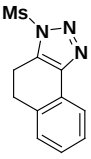
After successful demonstration of cascade EA/E and [3+2]-CA/H reactions from **88a** with TsN_3 **118a** under amine or amino acid-catalysis, we also investigated the amine or

amino acid-catalyzed cascade reaction of **88a** with the other azides[60] like MsN_3 **118b**, N_3CO_2Et **118c**, 4-$NO_2C_6H_4SO_2N_3$ (*p*NBSA) **118d**, 2-$NO_2C_6H_4SO_2N_3$ (*o*NBSA) **118e**, BnN_3 **118f** and $TMSN_3$ **118g**, but the diazotization or *N*H-1,2,3-triazole formation of the **88a** was inferior compared to TsN_3 **118a** as shown in Table 19, entries 1–7.

With the optimized reaction conditions in hand, the scope of the amino acid- and amine-catalyzed [3+2]-CA/H and EA/E cascade reactions was investigated. A series of substituted Hagemann's esters **88a-t** were reacted with 0.5 equivalents of azides **118a-b** catalyzed by 20-mol% of proline **14a** at 25 °C in DMSO (Table 20). Both aliphatic and aromatic substituted Hagemann's esters **88** were furnished the expected *N*H-1,2,3-triazoles **121** with excellent yields (Table 20). Yields of the cascade [3+2]-CA/H products **121** were increased by the prolonging reactions time up to 24 h and also water content of the DMSO solvent; and these are ideal examples for the bio-mimetic solvent induced cascade chemistry in organic reactions. For example, proline-mediated reaction of simple Hagemann's esters **88f**, **88t** and **88e**[61] with TsN_3 **118a** in DMSO at 25 °C for 1 h furnished the expected unhydrolyzed 1,2,3-triazoles **120fa**, **120ta** and **120ea** in 50%, 70% and 65% yields respectively as shown in Table 20, entries 11-13. But, unfortunately we are not observed the enantioselectivity in the L-proline **14a**-mediated cascade reaction of 6-substituted Hagemann's esters **88** with TsN_3 **118a**. Fascinatingly, reaction of 3,4-dihydro-*1H*-naphthalen-2-one **88u** with azides TsN_3 **118a** or MsN_3 **118b** at 25 °C for 1 h in DMSO under amino acid-catalysis furnished the expected 1,2,3-triazoles **120ua**/**120ub** in combination with **121ua**/**121ub** in almost quantitative yields with excellent regioselectivity as shown in Table 20. The products structures were confirmed by ^1H and ^{13}C NMR [for example see Fig. 19-21], mass analysis and regiochemistry of cascade products **120ua-ub/121ua-ub** was finally confirmed by X-ray structure analysis on **120ua** as shown in Scheme 16.[62]

Table 20: Chemically diverse libraries of *N*H-1,2,3-triazoles **121**



Entry	Product	Yield[%][a]	Entry	Product	Yield[%][a]
1	 **121aa**	94	8	 **121oa**	70
2	 **121sa**	90	9	 **121na**	65
3	 **121ba**	90	10	 **121qa**	55
4	 **121ia**	65	11	 **120fa**	50
5	 **121la**	75	12	 **120ta**	70
6	 **121ma**	80	13	 **120ea**	65
7	 **121ra**	70	14[b] 15[b][c]	 **120ua**  **120ub**	80 80

[a] Yield refers to the column-purified product. For the entries 1-10, reaction time is 12-24 h and for the entries 11-15, time is 0.75-1.0 h. [b] In both reactions, 15-20% of corresponding hydrolyzed *N*H-1,2,3-triazole **121ua** were isolated. [c] **118b** was used instead of **118a**.

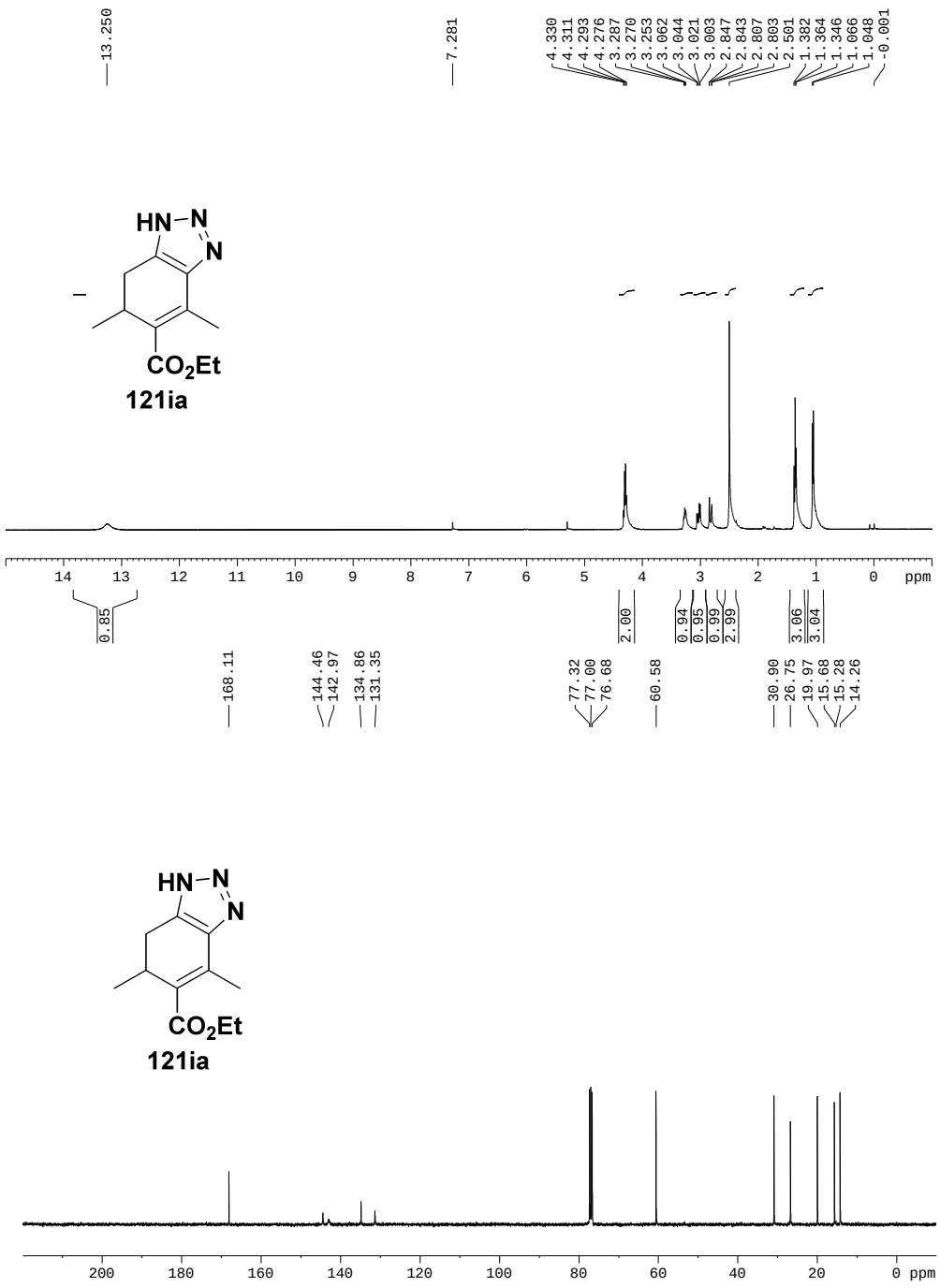


Figure-19: ^{1}H NMR and ^{13}C NMR Spectrum of product **121ia**.

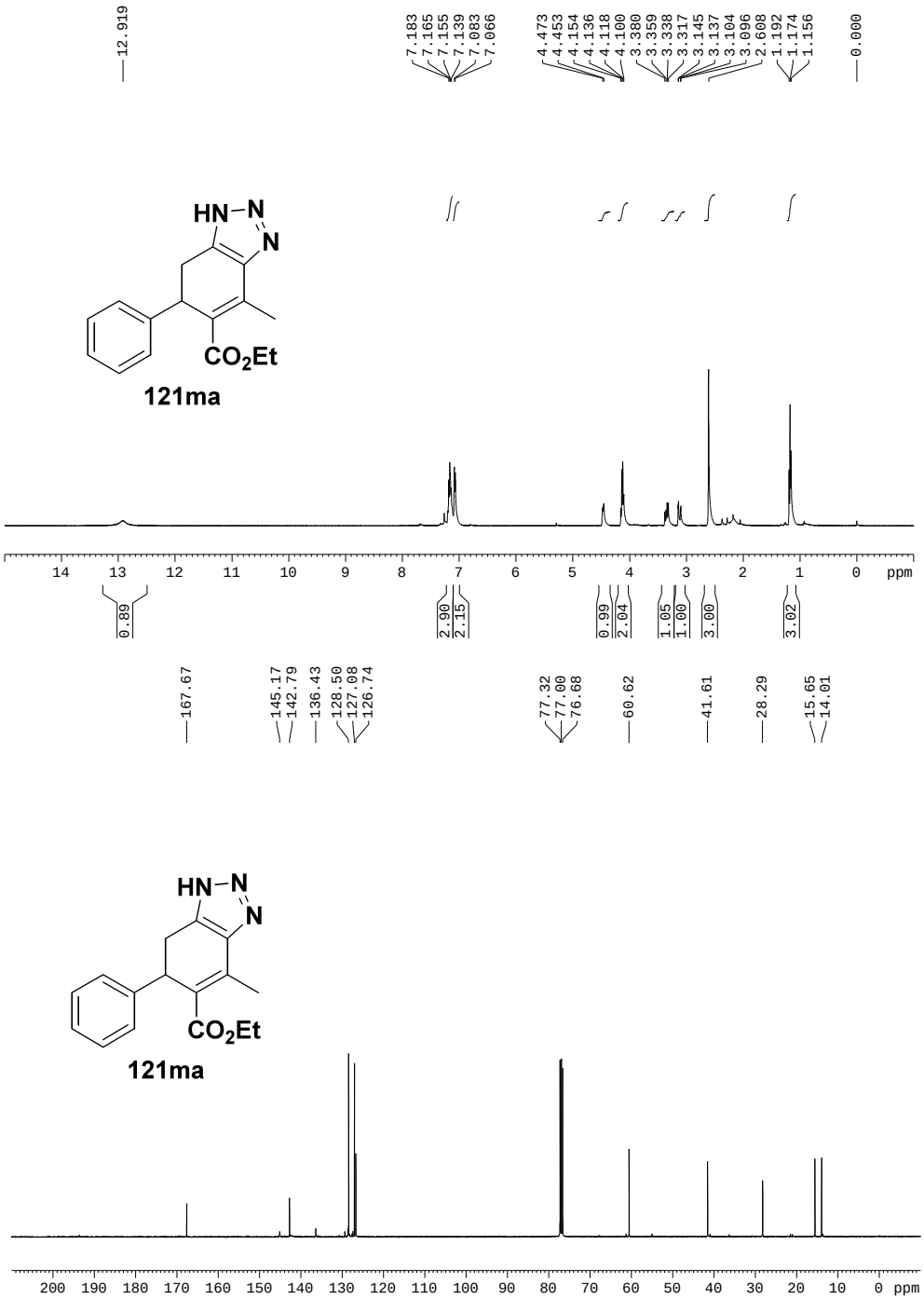


Figure-20: ^{1}H NMR and ^{13}C NMR Spectrum of product **121ma**.

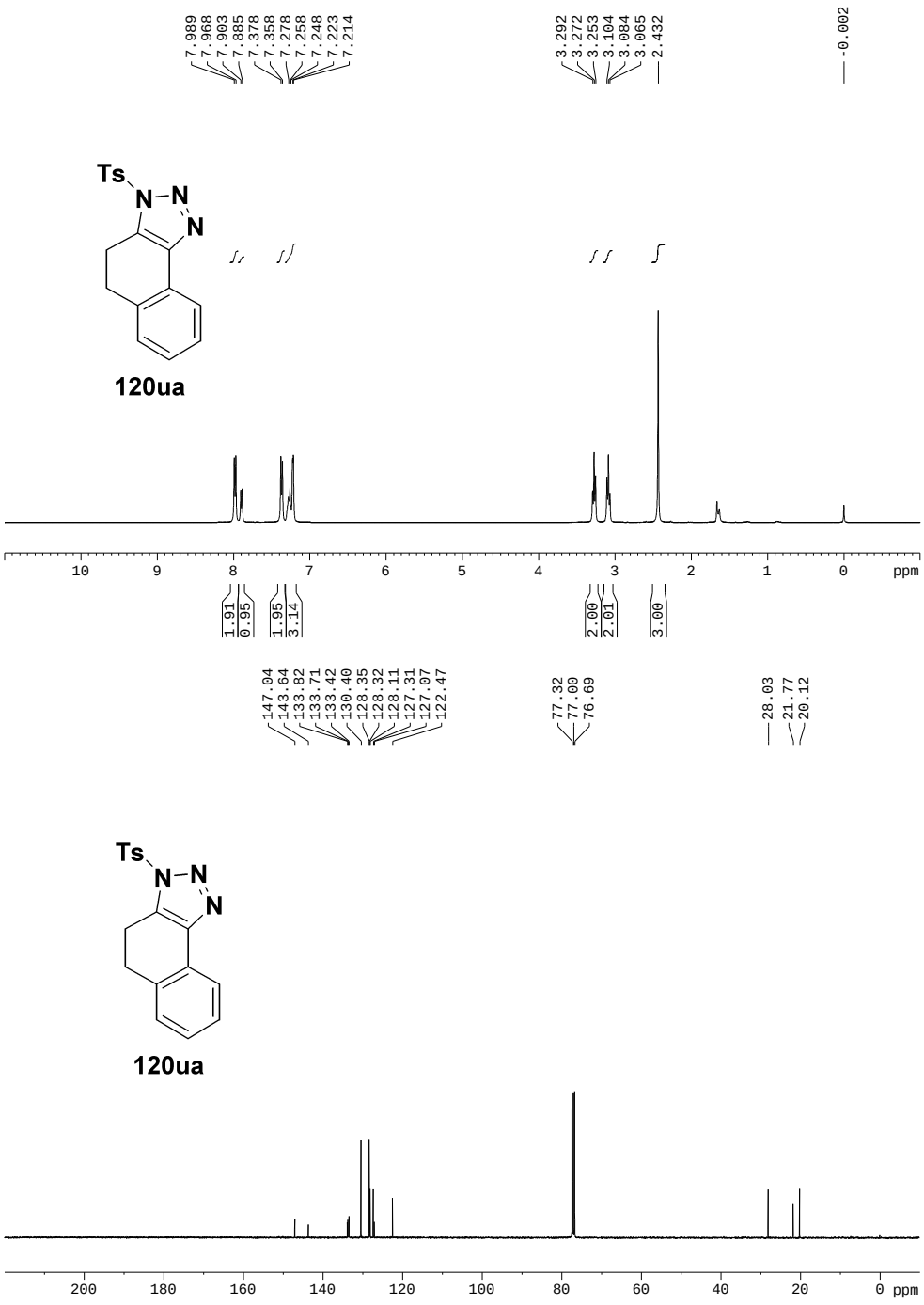
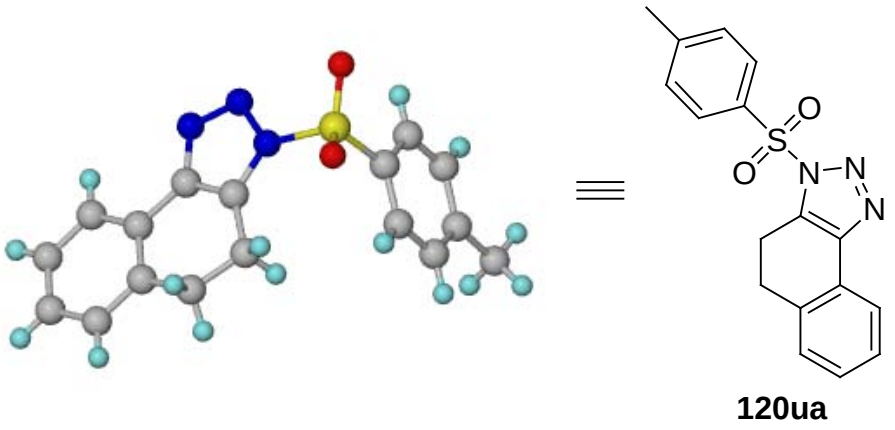


Figure-21: ^{1}H NMR and ^{13}C NMR Spectrum of product **120ua**.

Cascade products **120ua**/**121ua** would be very interesting model analogues for the studies of inhibitors of hMetAP2 as shown in eq 31.

Scheme 16: Crystal structure of 3-(toluene-4-sulfonyl)-4,5-dihydro-3H-naphtho[1,2-d][1,2,3]triazole (**120ua**).



120ua

We also generated the highly functionalized diversity oriented library of cascade EA/E products **119** under primary amine-catalysis. The results in Table 21 demonstrate the broad scope of this novel green methodology covering a structurally diverse group of Hagemann's esters **88a-s** and TsN_3 **118a** with many of the yields obtained being very good compared to tertiary amine-catalysis. Cascade EA/E reaction of Hagemann's esters **88a-s**, TsN_3 **118a** under benzylamine **2d**-catalysis furnished the diazo-products **119aa-119sa** in good yields (Table 21). Structure and regiochemistry of cascade EA/E products **119** was also confirmed by X-ray structure analysis on **119sa** as shown in Scheme 17.[63]

Scheme 17: Crystal structure of 3-diazo-2-methyl-4-oxo-cyclohex-1-enecarboxylic acid methyl ester (**119sa**).

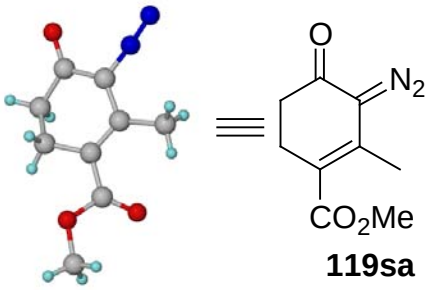
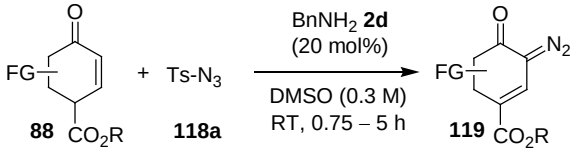
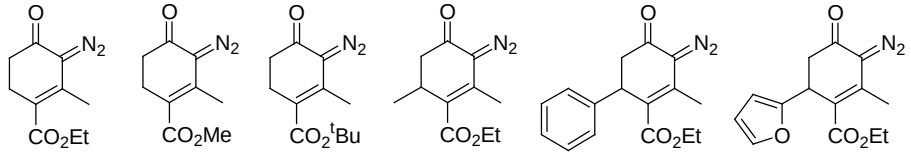


Table 21: Chemically diverse libraries of diazo-products **119**.[a]



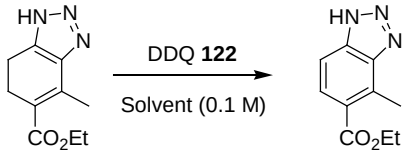


90% (**119aa**) 80% (**119sa**) 65% (**119ba**) 50% (**119ia**) 50% (**119ma**) 70% (**119ra**)

[a] Yield refers to the column-purified product.

The reaction of *N*H-1,2,3-triazole **121aa** with 1.5 to 2.0 equiv. of DDQ **122** in DCM or benzene as solvent at different temparatures did not furnished the expected aromatized *N*H-1,2,3-triazole **123aa** as shown in Scheme 18.

Scheme 18: Reaction optimisation for the aromatized *N*H-1,2,3-triazole **123aa** synthesis.

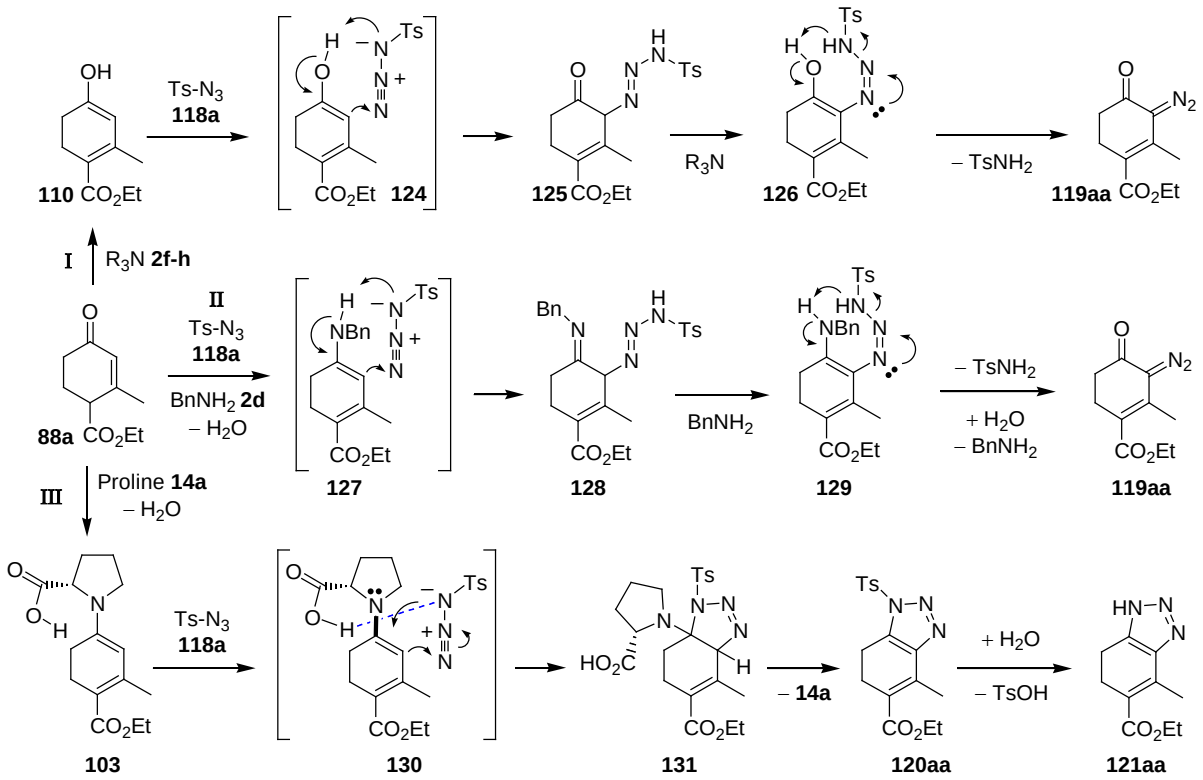


121aa **123aa**

Entry	Solvent [0.1 M]	DDQ **122** [equiv.]	Temp [^{o}C]	Time [h]	yield [%] **123aa**
1	Benzene	1.5	80	12	–
2	Benzene	2.0	80	24	–
3	Benzene	2.0	80	48	–
4	DCM	2.0	25	144	–

The possible reaction mechanism for the synthesis of cascade products **119**, **120** and **121** through reaction of Hagemann's ester **88a**, TsN_3 **118a** and amine/amino acid is illustrated in Scheme 19. The reaction mechanism can be divided into three categories (**I**, **II** and **III**) as catalyzed by three different amines as shown in Scheme 19. In the first category (**I**), reaction of tertiary amines with Hagemann's ester **88a** generates the push-pull dienol **110** based on reaction conditions.[1b] Reaction of push-pull dienol **110** with TsN_3 **118a** furnish the selectively amination product **125**, which will give product **126** via keto-enol tautomerism by treatment with basic amine. Rearrangement followed by elimination of toluene-4-sulfonamide of **126** converted into highly substituted diazo-product **119aa**. In the second category (**II**), reaction of primary amine $BnNH_2$ **2d** with Hagemann's ester **88a** generates the push-pull dienamine **127**,[1b] which on treatment with TsN_3 **118a** furnish the selectively amination product **128**, which will transform into product **129** via imine-enamine tautomerism by treatment with basic amine. Rearrangement followed by elimination of toluene-4-sulfonamide of **129** and hydrolysis of resulting imine gives to the highly substituted diazo-product **119aa**.

Scheme 19: Proposed reaction mechanism



In the third category (**III**), reaction of secondary amino acid proline **14a** with Hagemann's ester **88a** generates the push-pull dienamine **103**,[1b] which on treatment with TsN_3 **118a** furnish the selectively 7a-(2-carboxy-pyrrolidin-1-yl)-4-methyl-1-(toluene-4-sulfonyl)-3a,6,7,7a-tetrahydro-*1H*-benzotriazole-5-carboxylic acid ethyl ester **131** via concerted [3+2]-cycloaddition, which may transform into the product **120aa** through rapid elimination of proline **14a**. Possibility of weak interactions from acid group in transition state **130** will be the driving force to undergo concerted [3+2]-cycloaddition compare to **124**/**127** transition states. Solvent (DMSO) induced in situ hydrolysis of resulting 1,2,3-triazole **120aa** gives to the *N*H-1,2,3-triazole **121aa** in good yields as shown in Scheme 19. This in situ hydrolysis step is totally influenced by the water content of the DMSO solvent and not in the workup stage.

5.3 CONCLUSION

In summary, first time we have developed the synthesis of *N*H-1,2,3-triazole products **120** and **121** from simple starting materials via [3+2]-CA/H reactions under amino acid-catalysis. The cascade reaction proceeds in good yields with high selectivity using proline as the catalyst. Furthermore, we have demonstrated the bio-mimetic solvent induced hydrolysis in amino acid-catalyzed cascade reactions.

6. DIRECT ORGANOCATALYTIC ASYMMETRIC MICHAEL REACTIONS BASED ON THE PUSH-PULL DIENAMINE PLATFORM: SYNTHESIS OF HIGHLY SUBSTITUTED CHIRAL HAGEMANN'S ESTERS

6.1 INTRODUCTION

Asymmetric amino-catalysis has become one of the most important and wide spread area through iminium or enamine activation of carbonyl compounds.[29h,64] Among them, the direct Michael addition of saturated carbonyl compounds to β-nitrostyrenes through the enamine activation via amino-catalysis providing an expedient access for the development of functionalized molecules.[10b,29m,40b,65] Recently Barbas[10b] and his co-workers discovered the novel technology for organocatalytic asymmetric Michael addition of aldehydes/ketones with nitroolefins to provide a general route to a variety of Michael adducts in good yields with high enantioselectivity, which is known as "Barbas-Michael" reaction. The advent of this enamine based Barbas-Michael technology triggered a burst of activity in the synthesis of a huge chiral pool of Michael adducts through bio-mimetic enamine chemistry. After this discovery, the development of more general studies in the field of asymmetric Barbas-Michael reaction of carbonyls with nitroolefins was developed intensively and various effective organocatalytic methodologies have been developed.[29m,40b,65]

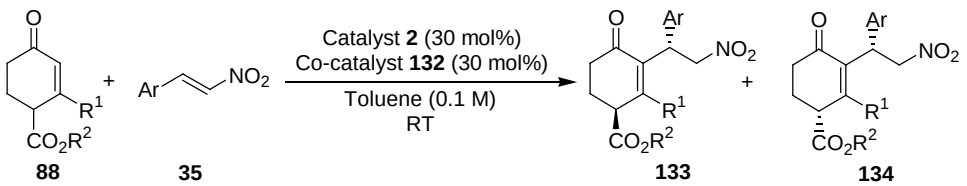
Interestingly, to the best of our knowledge asymmetric Michael addition of α,β-unsaturated carbonyl compounds having γ-hydrogen with nitroolefins via dienamine catalysis are not yet well studied. However, the amine-catalyzed Michael reaction of Hagemann's esters **88** with nitroolefins **35** was not known and the resulting products **133/134** have a wide range of uses in synthetic chemistry. Furthermore, there is no methodology available to prepare achiral compounds **133/134**. Herein, we have reporting a metal-free and novel technology for the asymmetric synthesis of substituted

2-alkyl-3-(2-nitro-1-aryl-ethyl)-4-oxo-cyclohex-2-enecarboxylic acid alkyl esters **133**/**134** using organocatalytic MA reactions from easily available Hagemann's esters **88**, nitroolefins **35** and amines **2** as shown in Scheme 20. As such the development of new and more general catalytic asymmetric methods are having significant interest, because of the synthetic versatility of the Michael adducts.

Recently, Chen *et al.* reported[26] the direct asymmetric Michael addition of α,β-unsaturated aldehydes to nitroolefins through the inversion of the inherent electrophilicity of α,β-unsaturated aldehydes via dienamine catalysis, but the direct asymmetric Michael addition of α,β-unsaturated ketones having γ-hydrogen to nitroolefins via dienamine catalysis is not known. Herein, we are reporting a metal-free and novel technology for the asymmetric synthesis of highly substituted functionalized esters **133/134** via the activation of novel chiral push-pull dienamines from Hagemann's esters **88** and nitroolefins **35** as shown in Scheme 20.

As part of our research program to engineer direct organocatalytic cascade reactions,[27] we have been interested in amine mediated *in situ* generation and application of novel push-pull dienamines/push-pull dienols in cascade reactions from Hagemann's esters with reactive electrophilic species for the formation of C-C and C-N bonds in single or multiple steps.[1] During our investigation for new reactive species for such processes, we decided to explore the potential ability of the nitrostyrenes **35** to participate in an amine catalyzed Michael addition (MA) with Hagemann's esters **88** as shown in Scheme 20. This result represents a good methodology for the preparation of functionalized chiral cyclohexenones and new reactivity of chiral push-pull dienamines. Herein, we described our findings regarding these new asymmetric Michael reactions.

Scheme 20: Direct asymmetric Michael reactions based on the push-pull dienamine platform.

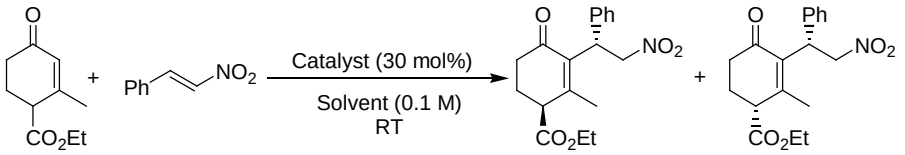


6.2 RESULTS AND DISCUSSION

We initiated our preliminary studies of the MA reactions by screening a number of known and novel organocatalysts for the Michael addition of Hagemann's ester **88a** by 1.5 equivalents of β-nitrostyrene **35a** and some representative results are shown in Table 22. Reaction of **88a** with 1.5 equiv. of β-nitrostyrene **35a** in DMSO solvent without catalyst furnished a 1:1 diastereomeric ratio of Michael products **133aa**/**134aa** in 61% yield with 0% ee within 28 hours (Table 22, entry 1). With this interesting result, we screened other solvents like toluene, DCM, THF, $CHCl_3$, CH_3CN, EtOH, MeOH, acetone, H_2O, 1,4-dioxane and isopropanol without adding catalyst, but these reactions didn't furnished Michael products **133aa**/**134aa** (results not presented in Table 22). We also screened various natural and unnatural amino acids such as (*S*)-(–)-indoline-2-carboxylic acid, hydroxy L-proline, L-phenylalanine, L-tyrosine, L-serine, L-threonine, L-leucine and O-*tert*-butyl-L-threonine for the Michael addition of Hagemann's ester **88a** with β-nitrostyrene **35a** in toluene but these amino acids didn't furnished Michael products **133aa**/**134aa** (results not presented in Table 22). Same reaction under 30-mol% of L-proline **14a**-catalysis to furnish a 1.5:1 *dr* of Michael products **133aa**/**134aa** in 30% yield with –12% ee and 10% ee in DMSO solvent (Table 22, entry 2). Same reaction of **88a** with 1.5 equiv. of **35a** under diamine **2i**-catalysis in toluene to furnish a 1.3:1 *dr* of Michael products **133aa**/**134aa** in 30% yield with 2% and 0% ee respectively (Table 22, entry 3). Bifunctional catalyst (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine/AcOH also catalyzed the MA reaction of **88a** with **35a** in DMSO to furnish a 1.5:1 ratio of Michael products **133aa**/**134aa** with good yield and 4% ee and –3% ee respectively (Table 22, entry 4). (*S*)-prolinol **2m** also catalyzed the MA reaction of **88a** with **35a** in $CHCl_3$ at 25 °C and 0 °C to furnish a 1.5:1 and 1.8:1 ratio of Michael products **133aa**/**134aa** in 75% and 40% yields with 0/3% ee and –31/0% ee respectively (Table 22, entries 5-6). Same reaction under **2m**-catalysis in toluene to furnish a 1:1.6 ratio of Michael products **133aa**/**134aa** in 60% yield with 11% ee and 2% ee, but under **2n**-catalysis in same solvent to furnish a 1:1.6 ratio of

Michael products **133aa**/**134aa** in 60% yield with 26% ee and 24% ee respectively (Table 22, entries 7-8). We also tested a number of primary and secondary

Table 22: Effect of solvent and catalyst on the direct asymmetric Michael reaction[a]



88a **35a** **133aa** **134aa**

Entry	Catalyst	Solvent	Time [h]	Yield [%][b]	*dr* ratio[c] **133aa/134aa**	*ee*[c] **133aa/134aa**
1	**–**	DMSO	28	61	1:1	0/0
2	**14a**	DMSO	8	30	1.5:1	–12/10
3	**2i**	Toluene	96	30	1.3:1	2/0
4[d]	**2i**	DMSO	2	60	1.5:1	4/–3
5	**2m**	$CHCl_3$	4	75	1.5:1	0/3
6[e]	**2m**	$CHCl_3$	48	40	1.8:1	–31/0
7	**2m**	Toluene	5	60	1:1.6	11/2
8	**2n**	Toluene	60	60	1:1.6	26/24
9	**2o**	Toluene	48	**–**	**–**	**–**
10	**2p**	Toluene	120	**–**	**–**	**–**
11	**47b**	Toluene	72	**–**	**–**	**–**
12[f]	**2q**	**Toluene**	**24**	**35**	**1.1:1**	**–49/–8**
13	**2r**	**Toluene**	**72**	**45**	**1.2:1**	**–55/–11**
14	**2s**	Toluene	48	**–**	**–**	**–**
15	**2t**	Toluene	60	66	1:1.2	42/40
16	**2u**	Toluene	60	70	1:1.2	19/13
17	**2v**	Toluene	96	**–**	**–**	**–**
18	**2w**	Toluene	96	**–**	**–**	**–**

[a] Reactions were carried out in 0.1 M solvent with 1.5 equiv. of nitro styrene **35a** relative to the Hagemann's ester **88a** in the presence of 30 mol% of catalyst. [b] Yield refers to the column purified product. [c] dr and ee determined by HPLC analysis. [d] 30 mol% Aceticacid also used. [e] Reaction performed at 0 °C. [f] Reaction was carried out in 0.15 M solvent.

amines such as chiral thiourea **2o**, L-2-benzhydryl-pyrrolidine **2p**, L-DPPOTMS **47b**, L-(3,5-$(CF_3)_2)_2$DPP **2s**, Q-NH_2 **2v** and CD-NH_2 **2w** as catalysts for the MA reaction of **88a** with **35a** in toluene though they didn't furnished Michael products **133aa**/**134aa**

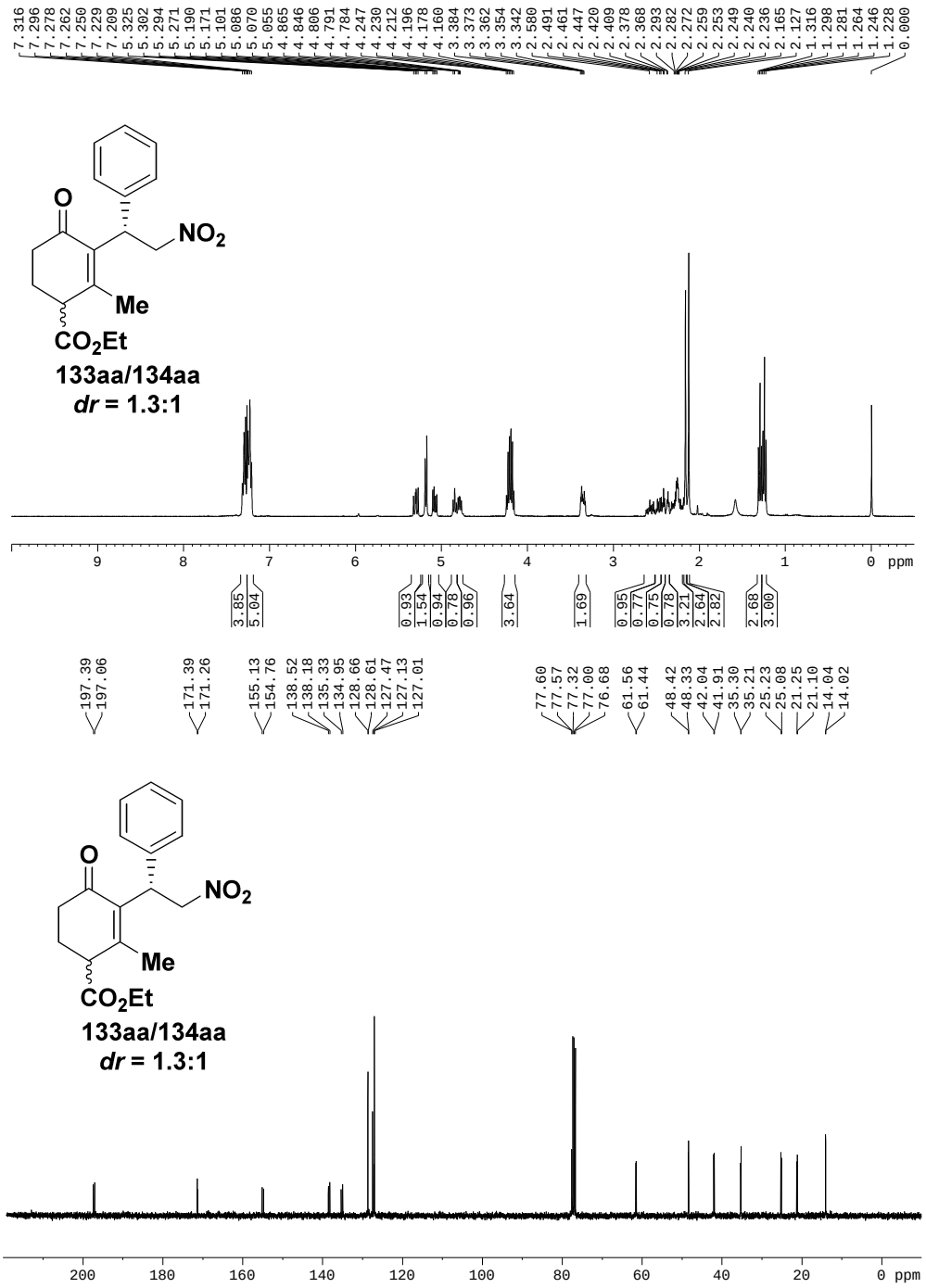
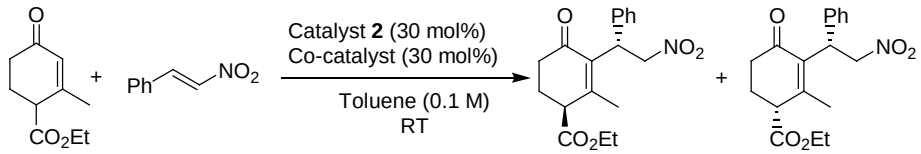


Figure-22: ^{1}H NMR and ^{13}C NMR Spectrum of product **133aa/134aa**.

(Table 22, entries 9-11, 14, 17 & 18). The Michael reaction of **88a** with **35a** under D-DPP **2q**-catalysis in toluene to furnish a 1.1:1 ratio of Michael products **133aa**/**134aa** in 35% yield with –49/–8% ee respectively as shown in entry 12, Table 22. Interestingly, same reaction with D-(3,5-Me_2)$_2$DPP **2r** in toluene to furnish a 1.2:1 ratio of Michael products **133aa**/**134aa** in 45% yield with –55/–11% ee respectively (Table 22, entry 13). Quinine (Q) **2t** catalyzed the MA reaction of **88a** with **35a** in toluene to furnish a 1:1.2 ratio of Michael products **133aa**/**134aa** in 66% yield with 42/40% ee respectively (Table 22, entry 15).

Table 23: Effect of co-catalyst on the direct asymmetric Michael reaction[a]



88a **35a** **133aa** **134aa**

Entry	Catalyst	Co-catalyst	Time [h]	Yield [%][b]	*dr* ratio[c] **133aa/134aa**	*ee*[c] **133aa/134aa**
1	**2q**	**132a**	72	50	1:1.3	–38/–31
2	**2q**	**132b**	48	70	1:1.0	–52/–31
3	**2q**	**132c**	36	44	1:1.4	–34/–30
4[d]	**2q**	**2o**	72	69	1.3:1	–66/2
5[d]	**2q**	**132d**	96	54	1.2:1	–57/7
6[e]	**2q**	**132b**	72	76	1:1.1	–42/–30
7	(***S***)**-2r**	**132e**	120	30	1:1.2	59/–4
8	(***S***)**-2r**	**132b**	**72**	**70**	**1.3:1**	**70/–7**
9[d]	**2r**	**2o**	72	66	1.2:1	–68/–12
10	**2r**	**132b**	72	80	1.1:1	–69/–15

[a] Reactions were carried out in solvent 0.1 M with 1.5 equiv. of nitrostyrene **35a** relative to the Hagemann's ester **88a** in the presence of 30 mol% of catalyst **2** and 30 mol% co-catal -yst. [b] Yield refers to the column purified product. [c] dr and ee determined by HPLC analys -is. [d] 10 mol% co-catalyst used.[e] Reaction performed at 50 ^{o}C.

To further improvement of ee/yield of Michael products **133aa**/**134aa**, we also screened co-catalyst effect with urea **132a**, thiourea **132b**, dicyclohexyl thiourea **132c**, chiral phosphoric acid **132d** and L-taddol **132e (**see Chart 3) on this MA reaction of

Hagemann's ester **88a** by 1.5 equivalents of β-nitrostyrene **35a** in toluene and some representative results are shown in Table 23. MA reaction of **88a** with 1.5 equiv. of **35a** under 30 mol% **2q**, along with 30 mol% urea **132a** as a co-catalyst furnished a 1:1.3 ratio of Michael products **133aa**/**134aa** in improved yield 50% with only –38% ee and –31% ee respectively (Table 23, entry 1).

Interestingly, same reaction conditions with 30-mol% thiourea **132b** as co-catalyst furnished a 1:1 ratio of Michael products **133aa**/**134aa** in 70% yield with –52/–31% ee (Table 23, entry 2). MA reaction of **88a** and **35a** with 30 mol% **2q** as catalyst and 30 mol% dicyclohexylthiourea **132c** as co-catalyst to furnish a 1:1.4 ratio of Michael products **133aa**/**134aa** in 44% yield with –34/–30% ee (Table 23, entry 3). MA reaction of **88a** and 1.5 equiv. of **35a** with 30 mol% **2q** and 10 mol% chiral thiourea **2o** as co-catalyst to furnish a 1.3:1 ratio of Michael products **133aa**/**134aa** in good yield 69% with –66/2% ee (Table 23, entry 4). MA reaction of **88a** and 1.5 equiv. of **35a** with 30 mol% **2q** and 10 mol% chiral phosphoric acid **132d** as co-catalyst to furnish a 1.2:1 ratio of Michael products **133aa**/**134aa** in 54% yield with –57/7% ee (Table 23, entry 5). But, under **2q** catalysis with thiourea **132b** as co-catalyst at 50 °C to furnish a 1.1:1 ratio of Michael products **133aa**/**134aa** in 76% yield with diminished ee values –42/–30% as compared to room temperature reaction (Table 23, entry 6). MA reaction of **88a** and 1.5 equiv. of **35a** with 30 mol% L-(3,5-Me_2)$_2$DPP as a catalyst and L-taddol **132e** as co-catalyst to furnish a 1:1.2 ratio of Michael products **133aa**/**134aa** in less yield 30% with 59% ee and –4% ee respectively (Table 23, entry 7). Same reaction with 30 mol% D-(3,5-Me_2)$_2$DPP **2r** as catalyst and 10 mol% chiral thiourea **2o** as co-catalyst to furnish a 1.2:1 ratio of Michael products **133aa**/**134aa** in 66% yield with –68% ee and –12% ee respectively (Table 23, entry 9). We envisioned the optimized condition to be 25 °C in toluene using 30 mol% L-(3,5-Me_2)$_2$DPP as catalyst and 30 mol% thiourea **132b** as co-catalyst to furnish highly substituted 1.3:1 ratio of Michael products **133aa**/**134aa** in 70% yield with 70% ee and –7% ee respectively (Table 23, entry 8). The product structure and regiochemistry was confirmed by ^{1}H NMR, ^{13}C NMR [for example see Fig. 22] and mass analysis.

Chart 2: Library of catalysts screened for the direct asymmetric Michael reactions.

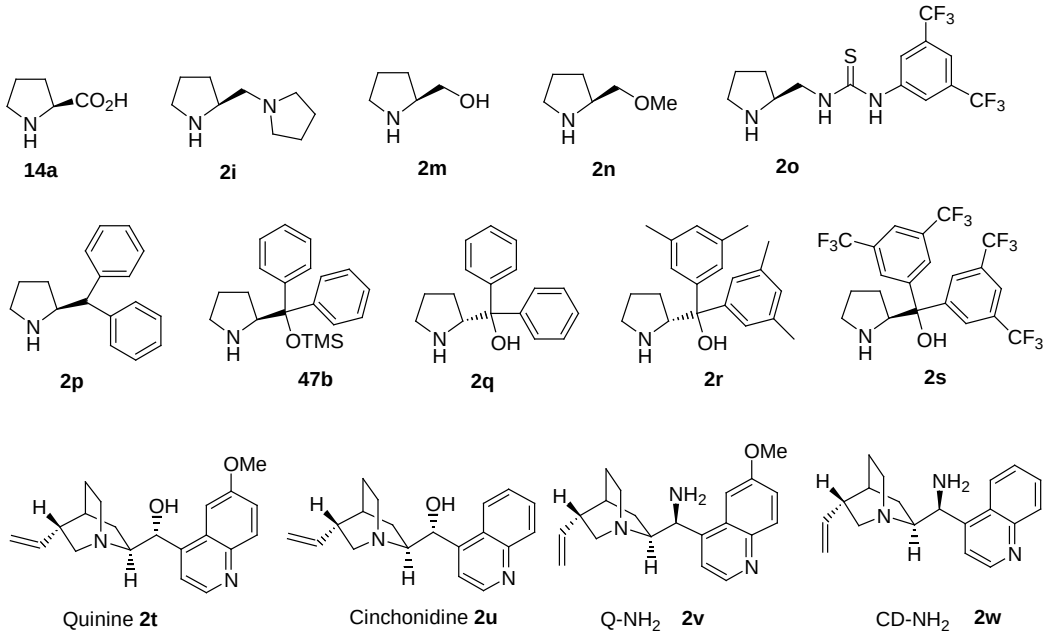
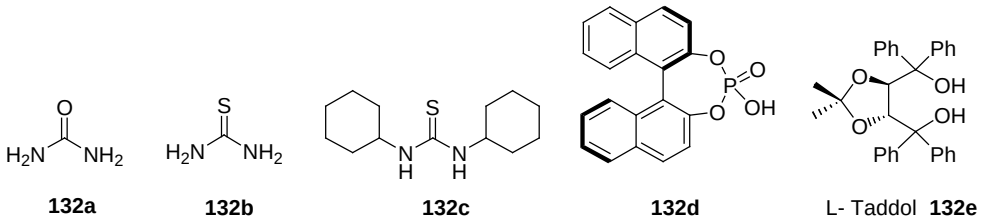
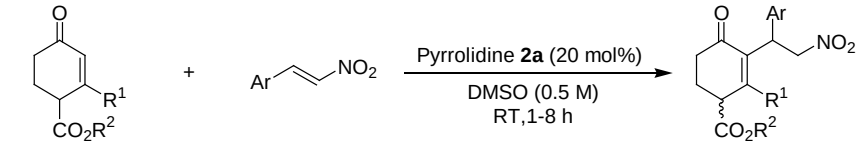


Chart 3: Library of co-catalysts screened for the direct asymmetric Michael reactions.

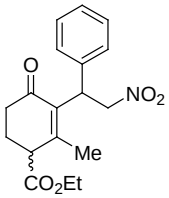


After successful demonstration and understanding of the MA reaction of **88a** with **35a** under amine catalysis, the scope and generality of MA reaction was investigated with functionalized Hagemann's esters **88a-b**, **88h** and **88s** and β-nitrostyrenes[66] **35a-j**. There is no methodology available to prepare achiral Michael products **133/134**, herein we prepared the library generation of the synthesis of achiral Michael products **133/134** in good yields under pyrrolidine **2a** catalysis (Table 24). MA reaction of Hagemann's esters **88a-b**, **88h** and **88s** with structurally diverse group of electron-donating, electron-withdrawing, halogenated and heterocyclic substituted

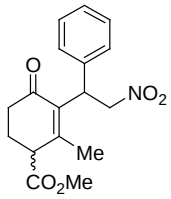
Table 24: Synthesis of achiral Michael products **133/134**.[a]



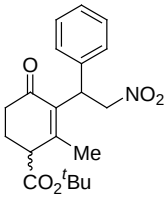
88 **35** **133/134**



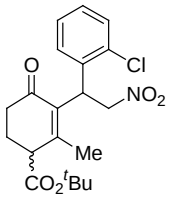
Yield:[b]60% (**133aa/134aa**)
dr[c] = 1.1:1



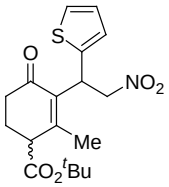
50% (**133sa/134sa**)
dr = 1.8:1



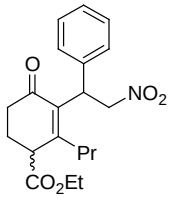
60% (**133ba/134ba**)
dr = 1.0:1



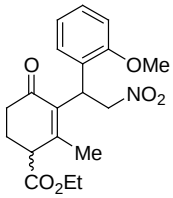
56% (**133bc/134bc**)
dr = 1.0:1



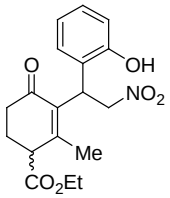
40% (**133bd/134bd**)
dr = 6.6:1



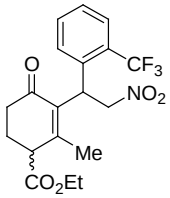
50% (**133ha/134ha**)
dr = 3.0:1



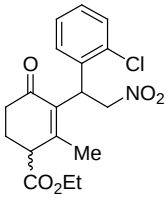
70% (**133ae/134ae**)
dr = 1.0:1



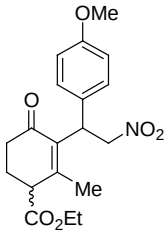
60% (**133af/134af**)
dr = 1.0:1



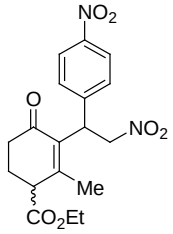
65% (**133ag/134ag**)
dr = 1.0:1



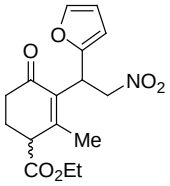
60% (**133ac/134ac**)
dr = 1.0:1



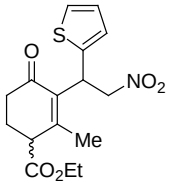
61% (**133ah/134ah**)
dr = 1.1:1



50% (**133ai/134ai**)
dr = 1.0:1



58% (**133aj/134aj**)
dr = 1.2:1



50% (**133ad/134ad**)
dr = 1.1:1

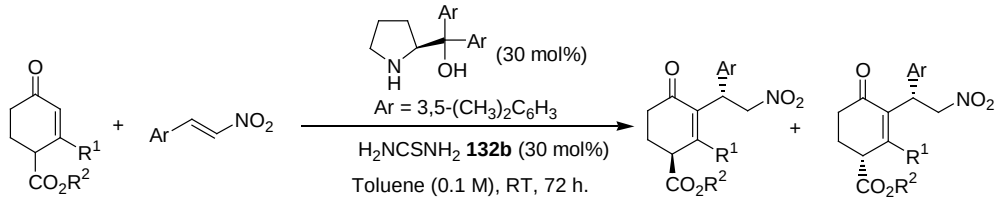
[a]Reactions were carried out in DMSO (0.5 M) with 1.2 equiv. of **35** relative to the Hagemann's ester **88** in the presence of 20 mol% pyrrolidine **2a**. [b]Yield refers to the column purified product. [c]Diastereomeric ratio determ -ined by NMR analysis.

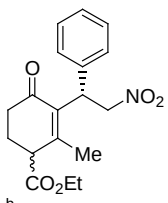
β-nitrostyrenes **35a-j** were generated expected Michael products **133/134** in good to excellent yields with 1.0:1 to 6.6:1 ratio's as shown in Table 24. The structure and regio-chemistry of achiral Michael products **133/134** were confirmed by NMR and mass analysis.

With the optimized reaction conditions in hand, for the asymmetric MA reaction of **88a** with **35a** under amine catalysis, we decided to investigate the asymmetric MA reaction with other functionalized Hagemann's esters **88b**, **88h** and **88s** with other functionalized β-nitrostyrenes **35b-j** in toluene to study the asymmetric synthesis of **133/134** products. A series of β-nitrostyrenes **35** containing different functional groups were reacted with Hagemann's esters catalyzed by 30 mol% of L-(3,5-Me_2)$_2$DPP with 30 mol% thiourea **132b** as co-catalyst at 25 °C for 72 h in toluene to furnish asymmetric MA products **133/134** in good yields with good to moderate ee's as shown in Table 25.

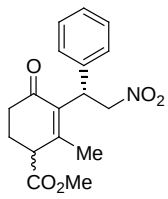
Asymmetric MA reaction catalyzed by 30 mol% L-(3,5-Me_2)$_2$DPP with 30 mol% thiourea **132b** on simple Hagemann's ester **88s** with β-nitrostyrene **35a** in toluene at 25 °C to furnish a 1:1.6 ratio of Michael products **133sa**/**134sa** in 60% yield with 61% ee and 11% ee respectively (Table 25, entry 2). The asymmetric MA reaction of β-nitrostyrene **35a** with *tert*-butyl ester **88b** catalyzed by L-(3,5-Me_2)$_2$DPP with co-catalyst **132b** in toluene at 25 °C to furnish a 2.1:1 ratio of Michael products **133ba**/**134ba** in 61% yield with 84% ee and 40% ee respectively (Table 25, entry 3). After this interesting result with *tert*-butyl ester **88b**, we decided to investigate the scope and limitations of the asymmetric MA reaction with other two β-nitrostyrenes **35c/d** with **88b** under L-(3,5-Me_2)$_2$DPP catalysis at the ambient conditions (Table 25, entries 4-5). Interestingly, MA reaction of 2-chloro-β-nitrostyrene **35c** with **88b** under L-(3,5-Me_2)$_2$DPP-catalysis to furnish a 1.5:1 ratio of Michael products **133bc**/**134bc** in 35% yield with 83/33% ee respectively as shown in Table 25, entry 4. MA reaction of 2-(2-nitro-vinyl)-thiophene **35d** with **88b** under L-(3,5-Me_2)$_2$DPP-catalysis to furnish a 5.2:1 ratio of Michael products **133bd**/**134bd** in 66% yield with 69/11% ee respectively as

Table 25: Synthesis of chiral Michael products **133/134**.[a]

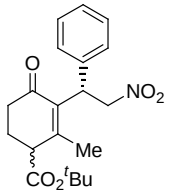




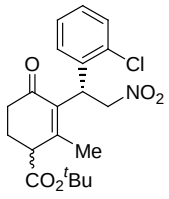
Yield:[b] 70% (**133aa/134aa**)
dr[c] = 1.3:1
ee[c] = 70%, –7%



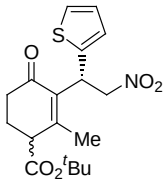
60% (**133sa/134sa**)
dr = 1:1.6
ee = 61%, 11%



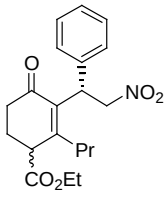
61% (**133ba/134ba**)
dr = 2.1:1
ee = 84%, 40%



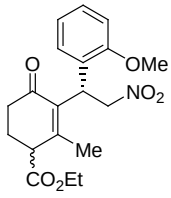
35% (**133bc/134bc**)
dr = 1.5:1
ee = 83%, 33%



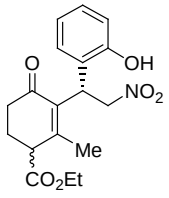
66% (**133bd/134bd**)[d]
dr = 5.2:1
ee = 69%, 11%



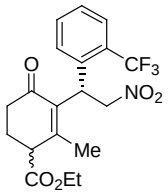
36% (**133ha/134ha**)
dr = 2.0:1
ee = 77%, 3%



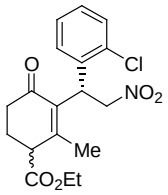
45% (**133ae/134ae**)
dr = 1.2:1
ee = 78%, 17%



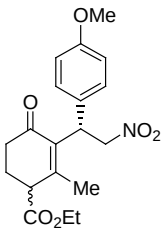
61% (**133af/134af**)
dr = 1.2:1
ee = 26%, 21%



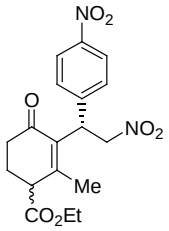
60% (**133ag/134ag**)
dr = 1:1.4
ee = 44%, 15%



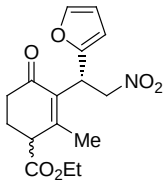
63% (**133ac/134ac**)
dr = 1.1:1
ee = 60%, 4%



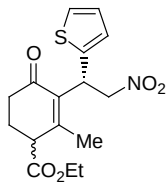
50% (**133ah/134ah**)
dr = 1:1.7
ee = 29%, 27%



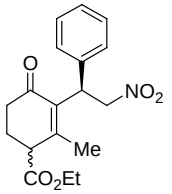
74% (**133ai/134ai**)
dr = 1:1.7
ee = 42%, 27%



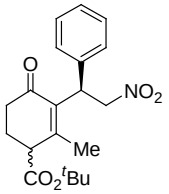
60% (**133aj/134aj**)
dr = 1.1:1
ee = 47%, 6%



60% (**133ad/134ad**)
dr = 1.5:1
ee = 41%, 12%



73%[e] (+)-**133aa/134aa**
dr = 1.2:1
ee = –70%, –14%



52%(–)-**133ba/134ba**[e,f]
dr = 2.6:1
ee = –85%, –8%

[a] Reactions were carried out in Toulene (0.1 M) with 1.5 equiv. of **35** relative to Hagemann's ester **88** in the presence of 30 mol% catalyst (***S***)-**2r** and 30 mol% co-catalyst **132b**.[b] Yield refers to the column purified product. [c] dr and ee determined by HPLC analysis. [d] Reaction time is 96 h. [e] 30 mol% **2r** used as catalyst. [f] Reaction performed in 0.2 M solvent.

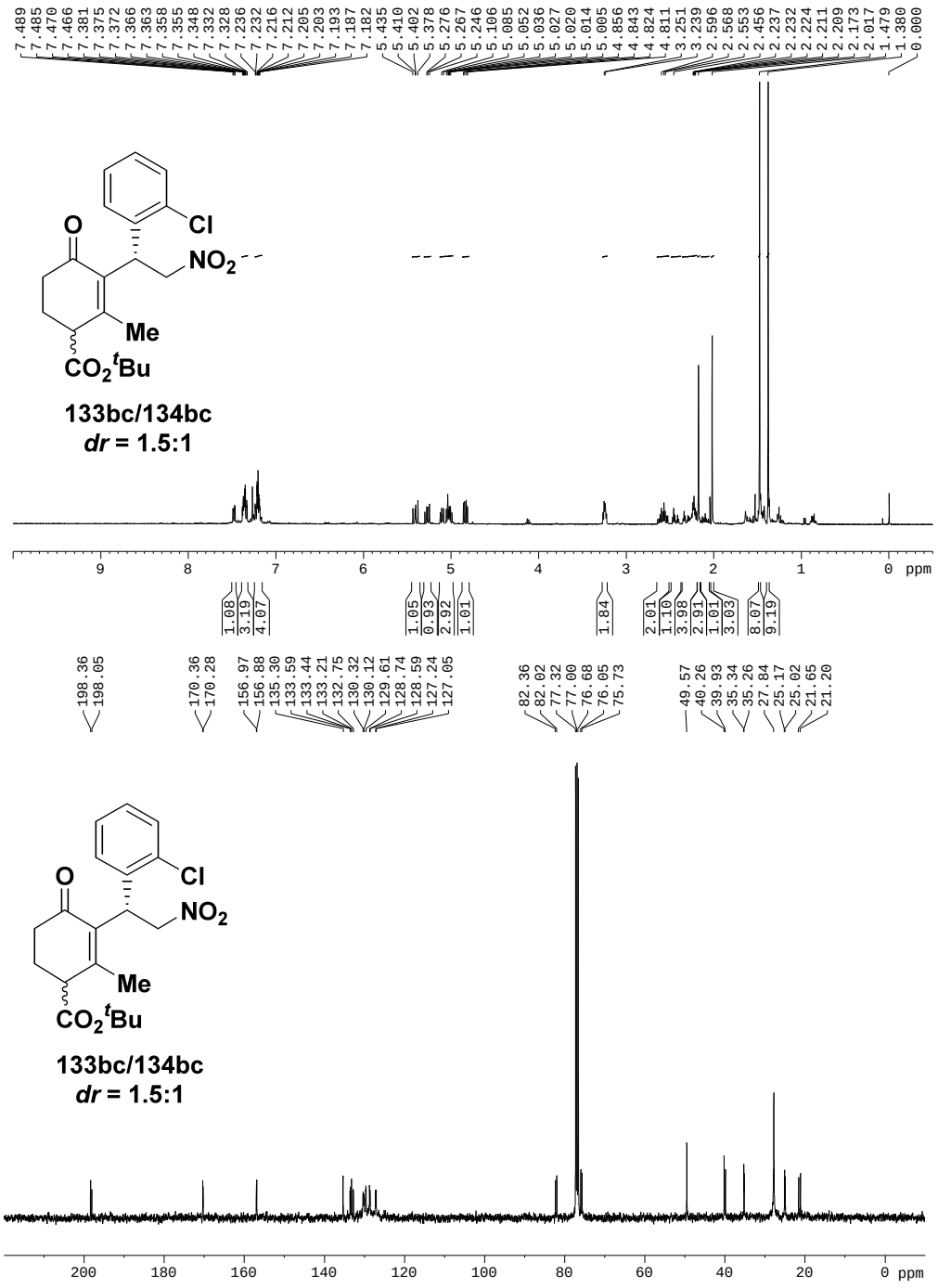


Figure-23: ^{1}H NMR and ^{13}C NMR Spectrum of product **133bc/134bc**.

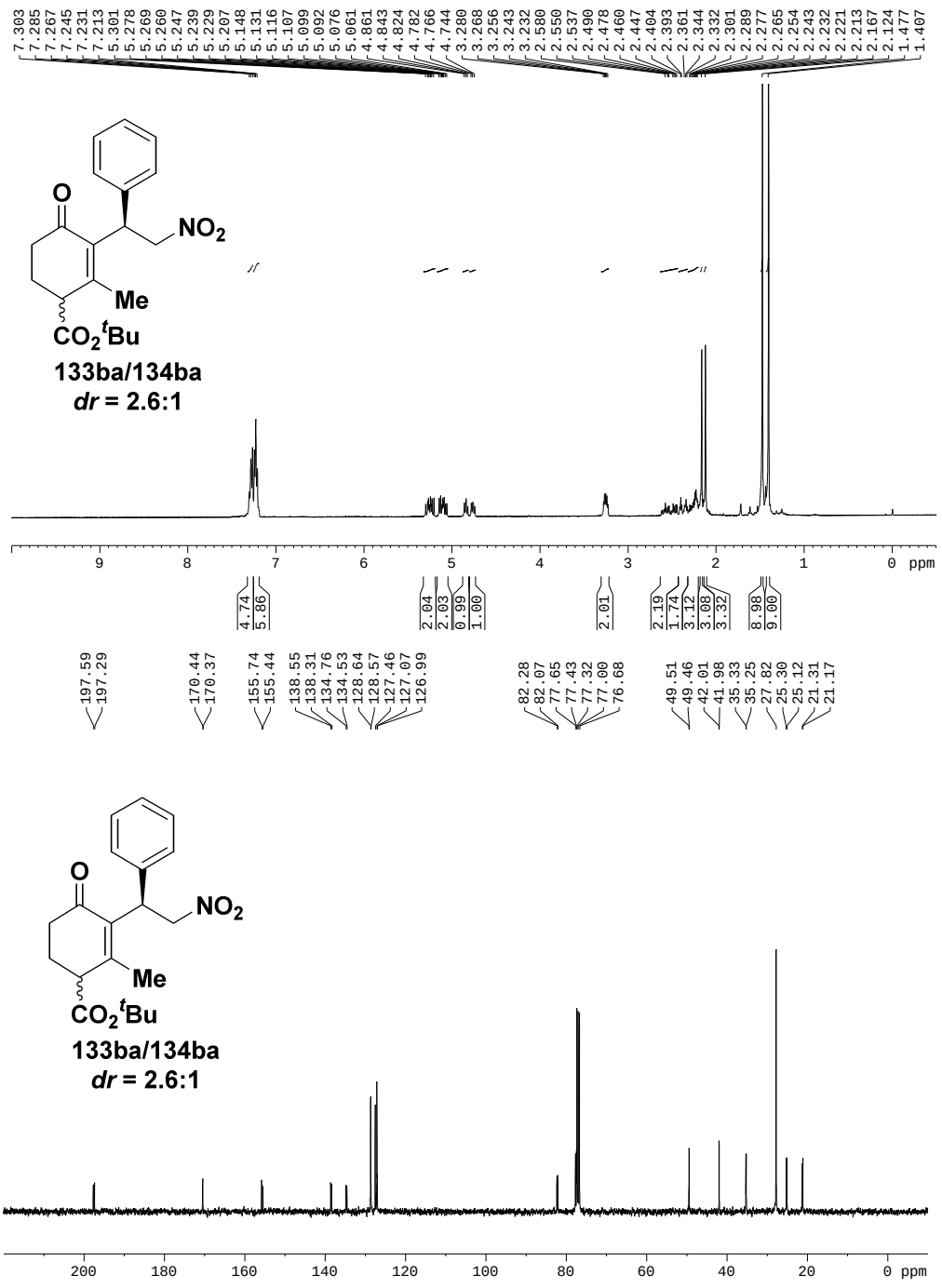


Figure-24: ^{1}H NMR and ^{13}C NMR Spectrum of product **133ba/134ba**.

shown in Table 25, entry 5. L-(3,5-Me_2)$_2$DPP-catalyzed asymmetric MA reaction of β-nitrostyrene **35a** with other Hagemann's ester **88h** in toluene at 25 °C to furnish a 2.0:1 ratio of Michael products **133ha**/**134ha** in 36% yield with 77% ee and 3% ee respectively (Table 25, entry 6). After these interesting results, we further decided to investigate the scope and limitations of the asymmetric MA reaction of Hagemann's ester **88a** with a range of β-nitrostyrenes **35** including functional groups containing electron-donating β-nitrostyrenes, electron-withdrawing β-nitrostyrenes, halogenated β-nitrostyrenes and heterocyclic β-nitrostyrenes under L-(3,5-Me_2)$_2$DPP catalysis with **132b** in toluene at the ambient conditions to test the diversity nature of the asymmetric MA reaction (Table 25).

Asymmetric MA reaction of Hagemann's ester **88a** with **35e** under L-(3,5-Me_2)$_2$DPP-catalysis to furnish a 1.2:1 ratio of Michael products **133ae**/**134ae** in 45% yield with 78/17% ee respectively as shown in Table 25, entry 7. Asymmetric MA reaction of Hagemann's ester **88a** with **35f** under L-(3,5-Me_2)$_2$DPP-catalysis to furnish a 1.2:1 ratio of Michael products **133af**/**134af** in 61% yield with 26/21% ee respectively as shown in Table 25, entry 8. Asymmetric MA reaction of Hagemann's ester **88a** with halogenated β-nitrostyrene **35g** under L-(3,5-Me_2)$_2$DPP-catalysis to furnish a 1:1.4 ratio of Michael products **133ag**/**134ag** in 60% yield with 44/15% ee respectively as shown in Table 25, entry 9. Asymmetric MA reaction of Hagemann's ester **88a** with **35c** under L-(3,5-Me_2)$_2$DPP-catalysis to furnish a 1.1:1 ratio of Michael products **133ac**/**134ac** in 63% yield with 60/4% ee respectively as shown in Table 25, entry 10. Interestingly, asymmetric MA reaction of 4-methoxy-β-nitrostyrene **35h** with Hagemann's ester **88a** under L-(3,5-Me_2)$_2$DPP-catalysis in toluene at 25 °C to furnish a 1:1.7 ratio of Michael products **133ah**/**134ah** in 50% yield with 29/27% ee respectively as shown in Table 25, entry 11. Asymmetric MA reaction of 4-nitro-β-nitrostyrene **35i** with Hagemann's ester **88a** under L-(3,5-Me_2)$_2$DPP-catalysis in toluene at 25 °C to furnish a 1:1.7 ratio of Michael products **133ai**/**134ai** in 74% yield with 42/27% ee respectively as shown in Table 25, entry 12. Generality of the L-(3,5-Me_2)$_2$DPP-catalyzed asymmetric MA reaction of Hagemann's esters **88** with β-nitrostyrenes **35** were confirmed by two more

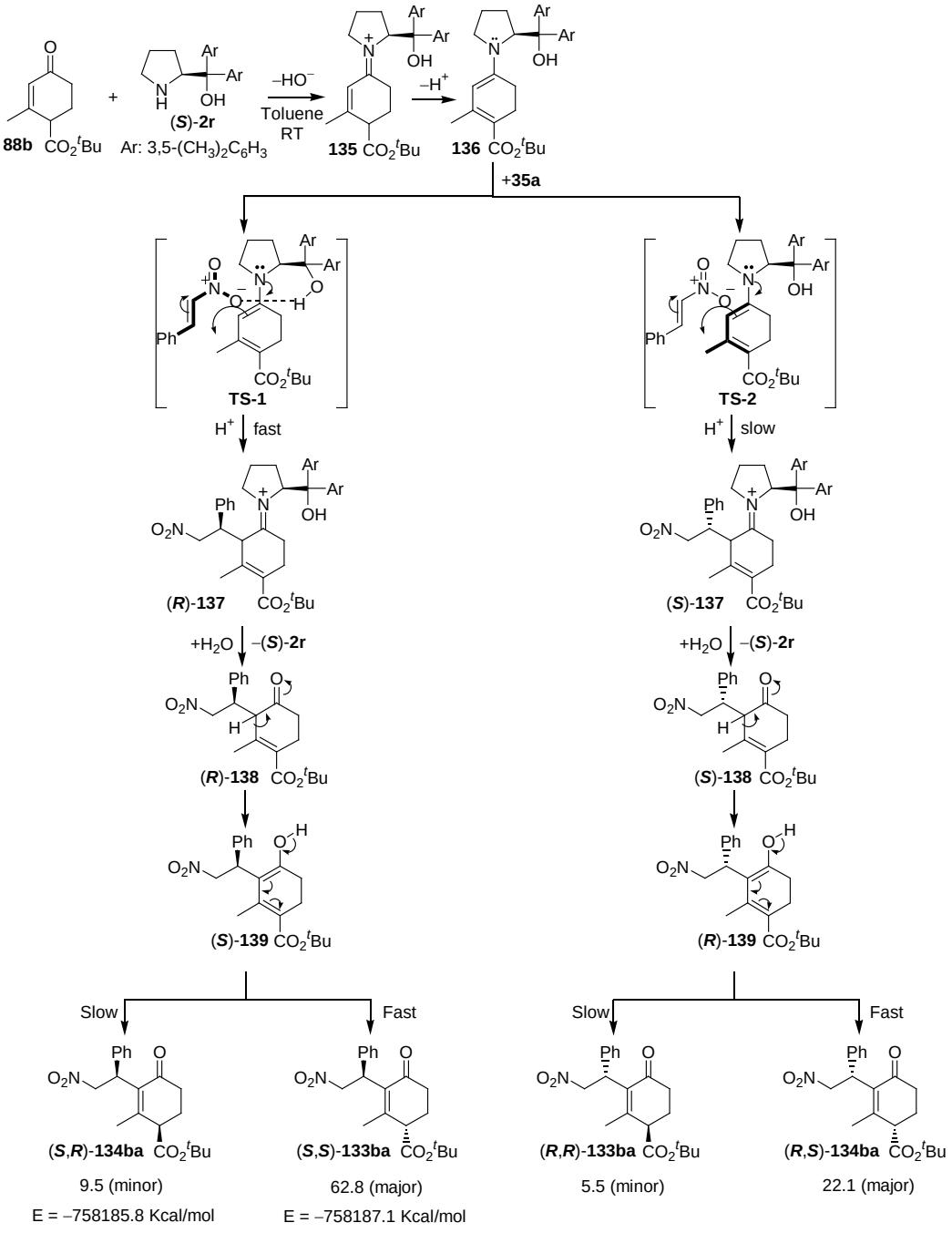
examples. Asymmetric Michael reaction of Hagemann's ester **88a** and heterocyclic β-nitrostyrene **35j** in toluene solvent to furnish a 1.1:1 ratio of Michael products **133aj**/**134aj** in 60% yield with 47/6% ee respectively as shown in Table 25, entry 13. Asymmetric Michael reaction of Hagemann's ester **88a** and **35d** in toluene solvent to furnish a 1.5:1 ratio of Michael products **133ad**/**134ad** in 60% yield with 41/12% ee respectively as shown in Table 25, entry 14.

To demonstrate the broad scope of this novel methodology for covering a structurally diverse group of Michael products **133**/**134,** we also used D-(3,5-Me_2)$_2$DPP **2r**/thiourea **132b** as catalyst in this asymmetric MA reaction with two examples as shown in Table 25, entries 15-16. Asymmetric MA reaction of Hagemann's ester **88a** and β-nirostyrene **35a** under D-(3,5-Me_2)$_2$DPP-catalysis to furnish a 1.2:1 ratio of Michael products (+)-**133aa**/**134aa** in 73% yield with –70/–14% ee respectively as shown in Table 25, entry 15. Asymmetric MA reaction of *tert*-butyl Hagemann's ester **88b** and β-nirostyrene **35a** under D-(3,5-Me_2)$_2$DPP-catalysis to furnish a 2.6:1 ratio of Michael products (–)-**133ba**/**134ba** in 52% yield with –85/–8% ee respectively as shown in Table 25, entry 16. The products structures and regiochemistry were confirmed by ^{1}H NMR, ^{13}C NMR [for example see Fig. 23-24] and mass analysis. The absolute configuration of products were established by correlation with Barbas-Michael reactions.[65]

The possible reaction mechanism for stereoselective synthesis of cascade products **133/134** through the reaction of *tert*-butyl Hagemann's ester **88b** and β-nitrostyrene **35a** under L-(3,5-Me_2)$_2$DPP catalysis is illustrated in Scheme 21. First, reaction of L-(3,5-Me_2)$_2$DPP with *tert*-butyl Hagemann's ester **88b** generates the imine cation **135**, which will transform into chiral push-pull dienamine **136** through proton elimination. Formation of the Michael product (*R*)-**137** through *re*-face attack of β-nitrostyrene **35a** with chiral push-pull dienamine **136** will be faster reaction as shown in **TS-1**. Formation of the Michael product (*S*)-**137** through *si*-face attack of β-nitrostyrene **35a** with chiral push-pull dienamine **136** will be slower reaction as shown in **TS-2**

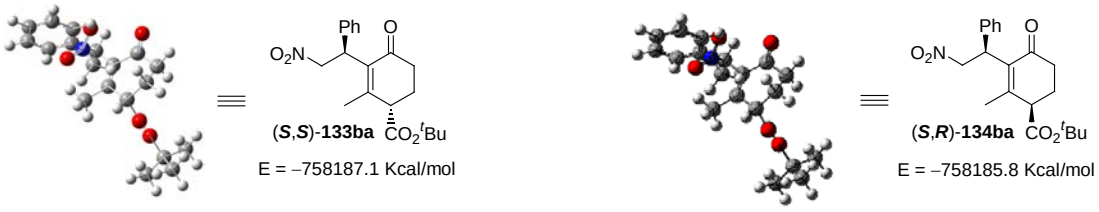
based on the hydrogen bonding interactions with OH. *In situ* hydrolysis of both the Michael products (*R*)-**137** and (*S*)-**137**

Scheme 21: Proposed reaction mechanism.



converted into highly substituted (*R*)-**138** and (*S*)-**138** under amine catalysis. Through the keto-enol tautomerism (*R*)-**138** and (*S*)-**138** will be converting to highly substituted (*S*)-**139** and (*R*)-**139** based on proton transfer reaction. Formation of the thermodynamically stable (*S, S*)-**133ba** product is faster reaction compared to formation of the kinetically stable (*S, R*)-**134ba** product. (*S, S*)-**133ba** product is a major isomer and (*S, R*)-**134ba** product is a minor isomer. The calculated heat of formation (ΔE) for the (*S, S*)-**133ba** product is 1.3 kcal/mol more than the (*S, R*)-**134ba** product as shown in Scheme 21 & 22. This result also strongly suggests that thermodynamically product (*S, S*)-**133ba** formation is more favorable than product (*S, R*)-**134ba** formation as revealed by DFT calculations. Formation of the (*R, S*)-**134ba** product is faster reaction compared to formation of the (*R, R*)-**133ba** product as shown in Scheme 21. In the compound (*R*)-**139** weak CH-π Interactions between the phenyl ring and olefinic methyl group and also anchoring effect of nitro group towards hydrogen facilitates the formation of (*R, S*)-**134ba** product as a major isomer. Formation of these four isomers are controlling the enantioselectivity of the reaction.

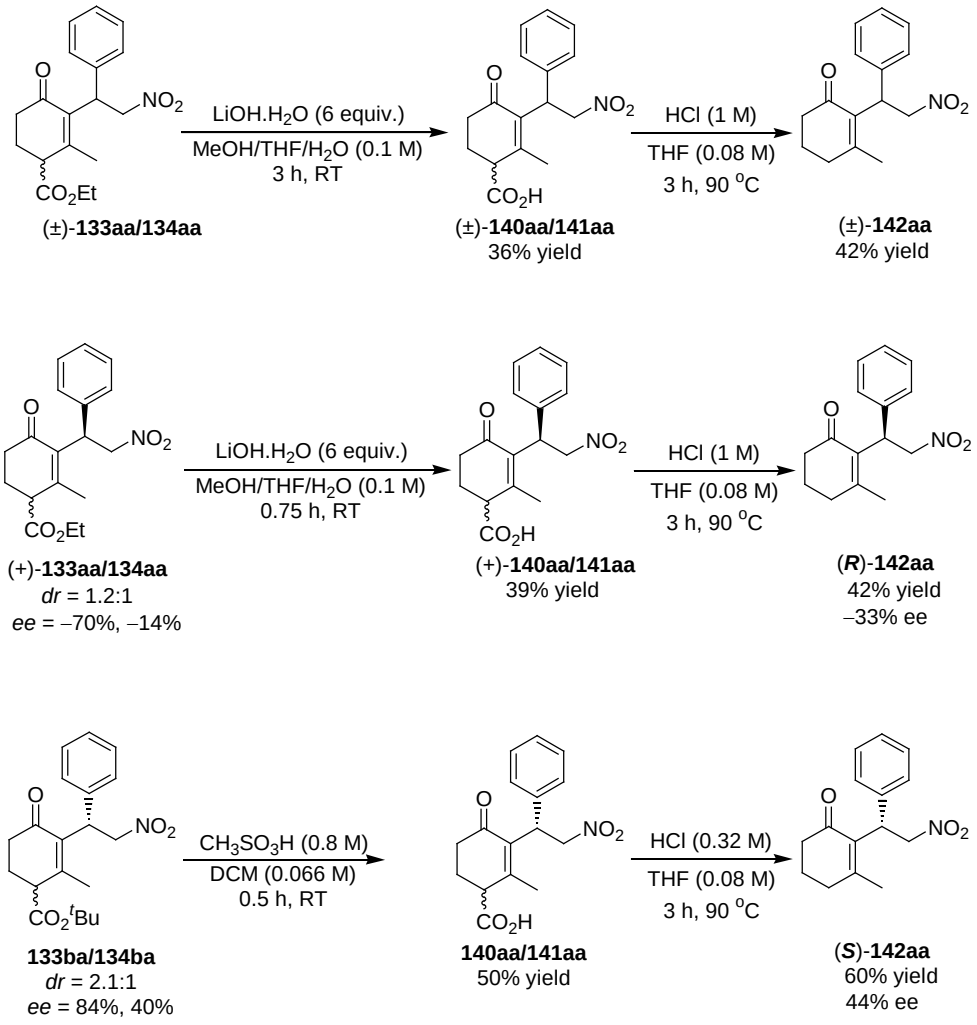
Scheme 22: Minimized structures of (*S, S*)-**133ba** and (*S, R*)-**134ba** based on DFT calculations.



The asymmetric MA reaction of β-nitrostyrene **35a** with *tert*-butyl ester **88b** catalyzed by L-(3,5-Me_2)$_2$DPP in toluene furnished a Michael products **133ba**/**134ba** with 84% ee and 40% ee and obtained the four possible isomers in a ratio of 9.5:62.8:5.5:22.1 (HPLC data). The reason for variation in the ee is because product (*R*,

S)-**134ba** is decreasing the ee value of product (*S*, *R*)-**134ba**. Another reason for decreasing the ee of product (*S*, *R*)-**134ba** may be due to the epimerization.

Scheme 23: Synthesis of functionalized cyclohexenone **142aa**.



After successful demonstration of the L-(3,5-Me_2)$_2$DPP catalyzed asymmetric MA reactions of Hagemann's esters **88** with β-nitrostyrenes **35**, we decided to study the utilization of the chiral Michael adducts **133/134** in the synthesis of functionalized chiral enones via acid/base catalysis[67] as shown in Scheme 23.

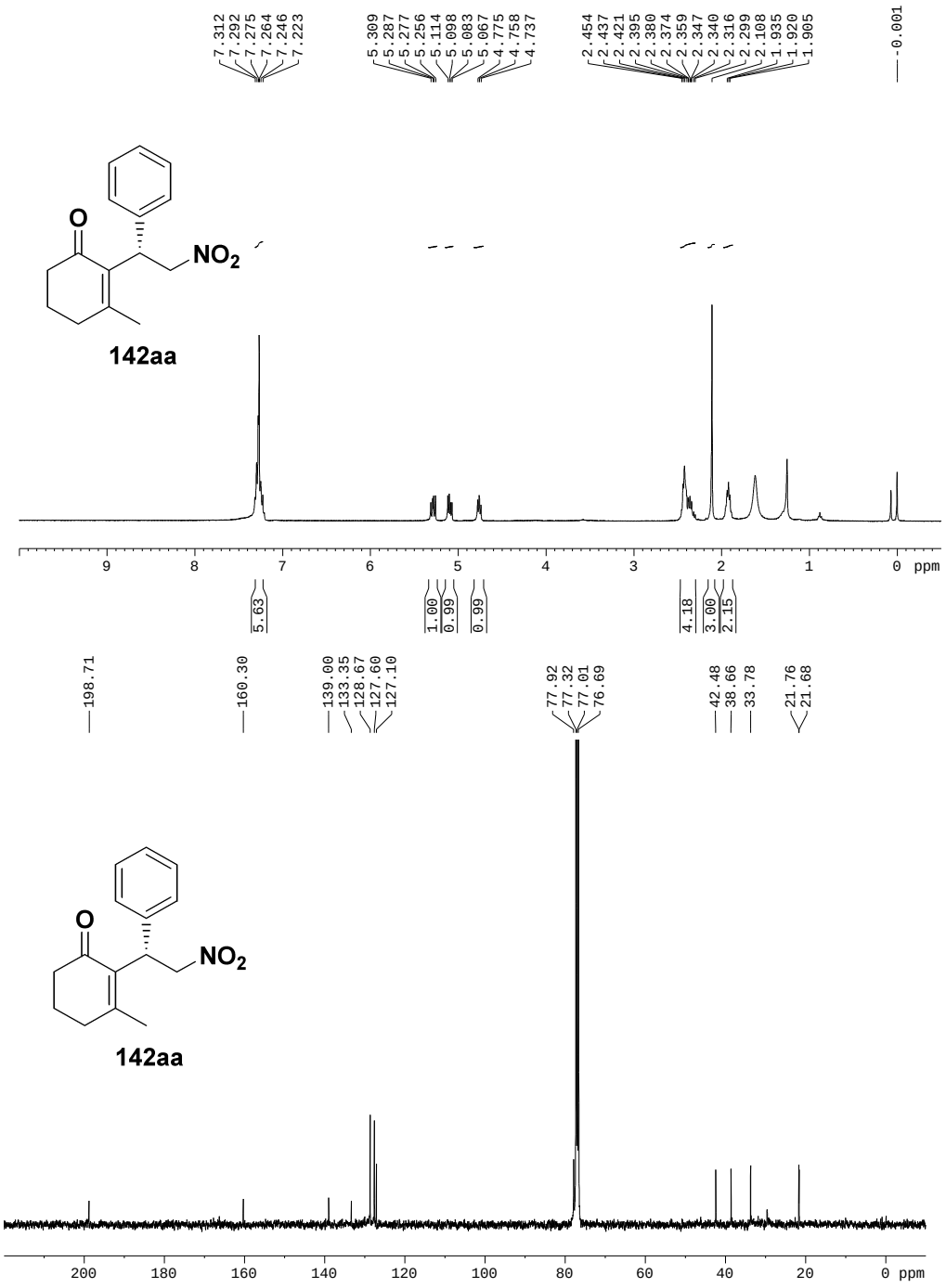


Figure-25: ^{1}H NMR and ^{13}C NMR Spectrum of product **142aa**.

Highly functionalized cyclohexenones (±)-**142aa**, (*R*)-**142aa** and (*S*)-**142aa** were synthesized from (±)-**133aa/134aa**, (+)-**133aa/134aa** and **133ba/134ba** in moderate yields with moderate ee's via acid/base catalysis as shown in Scheme 23. Reaction of 2-methyl-3-(2-nitro-1-phenylethyl)-4-oxo-cyclohex-2-enecarboxylic acid ethyl ester (±)-**133aa/134aa** with simple base ($LiOH.H_2O$) hydrolysis in MeOH/THF/H_2O solvent combination at RT furnished the keto acid (±)-**140aa/141aa** in 36% yield, which upon treatment with acid (HCl) in THF solvent furnished the decarboxylated product (±)-**142aa** in 42% yield as shown in Scheme 23. In a similar manner, (*R*)-**142aa** was synthesized from 2-methyl-3-(2-nitro-1-phenylethyl)-4-oxo-cyclohex-2-enecarboxylic acid ethyl ester (+)-**133aa/134aa** in 42% yield with –33% ee as shown in Scheme 23. Genaration of chiral cyclohexenones was studied by the synthesis of another enantiomer (*S*)-**142aa** as shown in Scheme 23. Reaction of 2-methyl-3-(2-nitro-1-phenylethyl)-4-oxo-cyclohex-2-enecarboxylic acid *tert*-butyl ester **133ba/134ba** with acidic (CH_3SO_3H) hydrolysis in DCM solvent at RT furnished the keto acid **140aa/141aa** in 50% yield, which upon treatment with acid (HCl) in THF solvent furnished the decarboxylated product (*S*)-**142aa** in 60% yield with 44% ee as shown in Scheme 23. The product structure and regiochemistry was confirmed by ^1H NMR, ^{13}C NMR [for example see Fig. 25] and mass analysis.

6.3 CONCLUSION

In summary, we have described chemo- and enantioselective process for the synthesis of highly substituted 2-alkyl-3-(2-nitro-1-arylethyl)-4-oxo-cyclohex-2-enecarboxylic acid alkyl esters **133/134** under amine catalysis. Here we described the L-(3,5-Me_2)$_2$DPP catalyzed asymmetric Michael reactions of Hagemann's esters **88** with nitroolefins **35** at ambient conditions. This novel asymmetric Michael reaction proceeds in good yields with high enantioselectivity using L-(3,5-Me_2)$_2$DPP as a catalyst along with thiourea **132b** as a co-catalyst. Furthermore, we demonstrated the application of chiral Michael products in the synthesis of highly functionalized cyclohexenones.

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49. X-ray crystal data of **107pa**: $C_{26}H_{27}ClN_2O_2$; MW = 434.95, Triclinic, space group p-1, with a = 10.602(2) Å, b = 10.735(2) Å, c = 11.281(2) Å, α = 77.344º, β = 67.507º, γ = 83.509º. CCDC-611666 contains the supplementary crystallographic data for this crystal structure.

50. Heat of formations (ΔH) of enamines **95** and **105** are calculated based on PM3 (MOPAC) calculations in *CS Chem3D Ultra* using wave function as closed shell (restricted) and minimize energy to minimum RMS Gradient of 0.100.

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58. X-ray crystal data of **120aa**: $C_{17}H_{19}N_3O_4S$; MW = 361.42, Monoclinic, space group *C* 2/c, with a = 8.0711(9) Å, b = 13.3560(16) Å, c = 32.165(4) Å, α = 90º, β = 90.516º, γ = 90º. CCDC-689189 contains the supplementary crystallographic data for this crystal structure.
59. X-ray crystal data of **121aa**: $C_{10}H_{13}N_3O_2$; MW = 207.23, Monoclinic, space group $P2_1/c$, with a = 13.520(9) Å, b = 8.995(6) Å, c = 9.344(6) Å, α = 90º, β = 107.868º, γ = 90º. CCDC-689190 contains the supplementary crystallographic data for this crystal structure.
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62. X-ray crystal data of **120ua**: $C_{17}H_{15}N_3O_2S$; MW = 325.39, Triclinic, space group p-1, with a = 6.7103(13) Å, b = 8.1812(16) Å, c = 14.451(3)αÅ, = 88.29º, β = 80.45º, γ = 82.94º. CCDC-690284 contains the supplementary crystallographic data for this crystal structure.

63. X-ray crystal data of **119sa**: $C_9H_{10}N_2O_3$; MW = 194.19, Monoclinic, space group $P2_1/c$, with a = 12.798(6) Å, b = 5.436(3) Å, c = 13.476(6) Å, α = 90°, β = 91.746°, γ = 90°. CCDC-689188 contains the supplementary crystallographic data for this crystal structure.

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8. EXPERIMENTAL SECTION

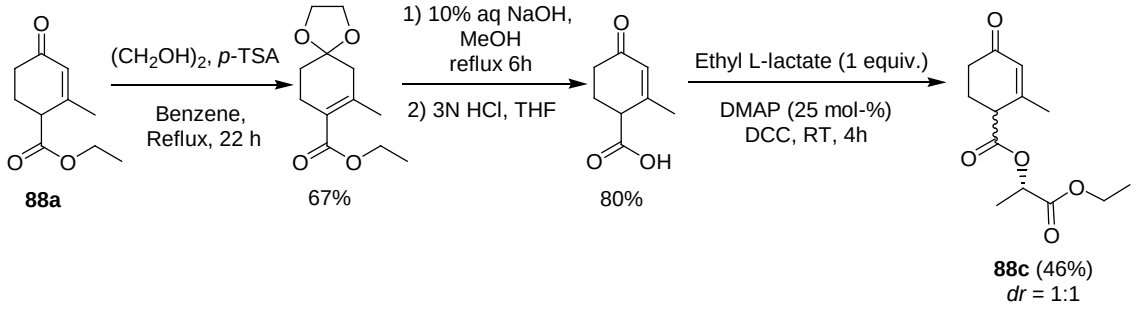
1: Synthesis of chiral Hagemann's esters 88c and 88d:

First step: A magnetically stirred solution of the Hagemann's ester **88a** (12 mmol), ethylene glycol (60 mmol) and a catalytic amount of *p*-TSA in dry benzene (75 mL) was refluxed for 22 h with a dean-stark water trap. Solvent benzene was distilled off; saturated aq. $NaHCO_3$ solution (15 mL) was added to the residue and extracted with ether (2 x 30 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure product was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate) as shown in Scheme E1.

Second step: A magnetically stirred solution of ketal ester (8 mmol), in methanol (15 ml) and 10% aq. NaOH (18 mL) was refluxed for 6 h. The reaction mixture was cooled and washed with DCM (2 x 10 mL). The *p*H of the reaction mixture was adjusted to 2 by stirring crude reaction mixture with 3 mL of 3N aq. HCl in THF (10 mL) for 0.5 h at 25 °C to furnish the keto-acid, which is extracted with dichloromethane (2 x 20 mL). The combined organic layers were dried with Na_2SO_4, and pure product was obtained by column chromatography (silica gel, pure ethyl acetate) as shown in Scheme E1.

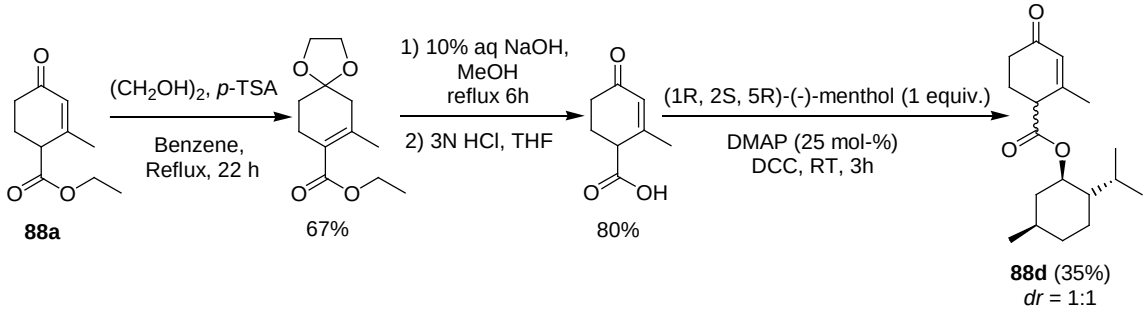
Third step-1: A 10 mL oven-dried round bottom flask equipped with a stirring bar was charged with keto acid (2 mmol) and DMAP (25 mol-%) in dry CH_2Cl_2 (10 mL) and added ethyl L-lactate (2 mmol) and DCC (2 mmol). The reaction mixture was stirred under N_2 at room temperature for 4 h. The crude reaction mixture was worked up with aqueous NH_4Cl solution and the aqueous layer was extracted with dichloromethane (2 x 20 mL). DCU was removed by filtration and combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure product **88c** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate) as shown in Scheme E1.

Scheme E1: Synthesis of Hagemann's ester **88c**

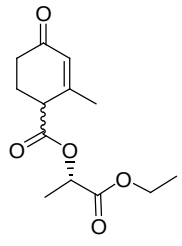


Third step-2: A 10 mL oven-dried round bottom flask equipped with a stirring bar was charged with keto acid (2 mmol) and DMAP (25 mol-%) in dry CH_2Cl_2 (10 mL) and added (1*R*, 2*S*, 5*R*)-(–)-menthol (2 mmol) and DCC (2 mmol). The reaction mixture was stirred under N_2 at room temperature for 3 h. The crude reaction mixture was worked up with aqueous NH_4Cl solution and the aqueous layer was extracted with dichloromethane (2 x 20 mL). DCU was removed by filtration and combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure product **88d** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate) as shown in Scheme E2.

Scheme E2: Synthesis of Hagemann's ester **88d**



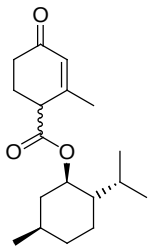
(*S*)-1-ethoxy-1-oxopropan-2-yl 2-methyl-4-oxocyclohex-2-enecarboxylate (88c):



88c
dr = 1:1

Purified by column chromatography using EtOAc/hexane and isolated as a liquid. $[\alpha]^{25}_{D}$ = –16.0 (*c* 0.3, $CHCl_3$) IR (neat): ν_{max} 2926, 2852, 1741 (O-C=O), 1672 (C=O), 1252, 1211, 1177, 1134, 1097 cm^{-1}; ^1H NMR ($CDCl_3$, 1:1 ratio of diastereomers) δ 5.99 (2H, s, 2 X olefinic-*H*), 5.12 (2H, q, *J* = 7.2 Hz), 4.20 (4H, q, *J* = 6.8 Hz), 3.34 (2H, brs), 2.67-2.54 (2H, m), 2.43-2.24 (6H, m), 2.07 (3H, s, olefinic-C*H*$_3$), 2.06 (3H, s, olefinic-C*H*$_3$), 1.52 (6H, d, *J* = 7.2 Hz), 1.27 (6H, t, *J* = 7.2 Hz, 2 X OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135, 1:1 ratio of diastereomers) δ 198.3 (2 X C, C=O), 171.1 (C, O-C=O), 171.0 (C, O-C=O), 170.3 (C, O-C=O), 170.2 (C, O-C=O), 156.5 (2 X C), 128.73 (CH), 128.66 (CH), 69.4 (CH), 69.3 (CH), 61.6 (2 X CH_2), 45.6 (2 X CH), 34.1 (CH_2), 34.0 (CH_2), 26.1 (CH_2), 26.0 (CH_2), 23.5 (CH_3, olefinic-*C*H_3), 23.4 (CH_3, olefinic-*C*H_3), 16.8 (2 X CH_3), 14.1 (2 X CH_3, OCH_2CH_3).

(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 2-methyl-4-oxocyclohex-2-enecarboxylate (88d):

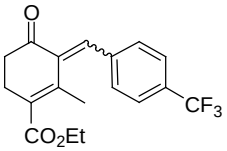


88d
dr = 1:1

Purified by column chromatography using EtOAc/hexane and isolated as a liquid. $[\alpha]^{25}_{D}$ = –62.4 (*c* 0.3, $CHCl_3$) IR (neat): ν_{max} 2982, 2361, 2336, 1730 (O-C=O), 1673 (C=O), 1376, 1254, 1186, 1037, 857cm^{-1}; ^1H NMR ($CDCl_3$, 1:1 ratio of diastereomers) δ 5.95 (2H, s, 2 X olefinic-*H*), 4.76-4.69 (2H, m), 3.24 (2H, t, *J* = 4.4 Hz), 2.57-2.47 (2H, m), 2.37-2.30 (4H, m), 2.25-2.16 (2H, m), 2.00 (6H, s, 2 X olefinic-C*H*$_3$), 1.97-1.96 (2H, m), 1.84-1.78 (4H, m), 1.70-1.66 (4H, m), 1.50-1.36 (4H, m), 1.09-0.96 (4H, m), 0.91-0.87 (14H, m), 0.74 (6H, dd, *J* = 6.8, 1.6 HZ); ^{13}C NMR ($CDCl_3$, DEPT-135, 1:1 ratio of diastereomers) δ 198.4 (2 X C, C=O), 171.1 (2 X C, O-C=O), 157.22 (C), 157.15 (C), 128.4 (CH), 128.3 (CH), 75.44 (CH), 75.37 (CH), 46.8 (2 X CH), 46.5 (CH), 46.3 (CH), 40.8 (CH_2), 40.6 (CH_2), 34.3 (CH_2), 34.2 (CH_2), 34.1 (2 X CH_2), 31.3 (2 X CH), 26.3 (2 X CH), 26.2 (2 X CH_2), 23.43 (CH_3), 23.39 (CH_3), 23.1 (2 X CH_2), 21.9 (2 X CH_3), 20.7 (2 X CH_3), 16.0 (2 X CH_3).

2a: Glycine-catalyzed Claisen-Schmidt reactions: In an ordinary glass vial equipped with a magnetic stirring bar, to 0.5 mmol of the Hagemann's ester **88a** was added 1.0 mL of DMSO solvent, and then the catalyst glycine **14d** (0.1 mmol, 7.5 mg) was added and then 0.5 mmol of aldehyde **28b-28m** was added in one-portion and the reaction mixture was stirred at 25 °C for the time indicated in Table 4. The crude reaction mixture was worked up with aqueous NH_4Cl solution and the aqueous layer was extracted with dichloromethane (2 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The pure products **89ab-89am** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

2-Methyl-4-oxo-3-(4-trifluoromethyl-benzylidene)-cyclohex-1-enecarboxylic acid ethyl ester (89ad): Prepared following the procedure **2a** and purified by column chromatography using EtOAc/hexane and isolated as a light yellow solid. Mp 54 °C; IR (neat): ν_{max} 2984, 1703 (C=O and O-C=O), 1456, 1324, 1241, 1168, 1126, 1064, 1017 and 838 cm^{-1}; ^1H NMR ($CDCl_3$, 2:1 ratio of *E/Z* isomers) δ 7.59 (4H, d, *J* = 8.4 Hz), 7.53 (2H, d, *J* = 8.0 Hz), 7.44-7.40 (3H, m), 6.95 (1H, s, olefinic-*H*), 4.26 (4H, q, *J* = 7.2 Hz, 2 x OC*H*$_2$CH$_3$), 2.83-2.78 (4H, m), 2.68 (2H, t, *J* = 6.4 Hz), 2.47 (2H, t, *J* = 6.4 Hz), 2.24 (3H, s, olefinic-C*H*$_3$), 1.94 (3H, s, olefinic-C*H*$_3$), 1.33 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$), 1.32 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, 2:1 ratio of *E/Z* isomers) δ 201.4 (C, C=O), 200.5 (C, C=O), 168. 4 (C, O-C=O), 167.1 (C, O-C=O), 142.6 (C), 139.9 (C), 139.5 (C), 139.3 (C), 138.9 (C), 138.1 (C), 134.8 (CH), 134.4 (CH), 131.2 (C), 130.8 (CF_3, q, *J* = 33.0 Hz), 129.9 (2 x CH), 129.6 (C), 129.4 (2 x CH), 125.2 (2 x CH, q, *J* = 3.0 Hz), 124.9 (2 x CH, q, *J* = 3.0 Hz), 122.6 (C), 122.4 (C), 60.9 (CH_2, OC*H*$_2$CH$_3$), 60.8 (CH_2, OC*H*$_2$CH$_3$), 39.3 (CH_2), 34.7 (CH_2), 27.2 (CH_2), 23.1 (CH_2), 20.4 (CH_3, olefinic-C*H*$_3$), 16.5 (CH_3, olefinic-C*H*$_3$), 14.2 (2 x CH_3, OCH$_2$C*H*$_3$); LRMS m/z 338.30 (M^+), calcd $C_{18}H_{17}F_3O_3$ 338.1130; Anal. calcd for $C_{18}H_{17}F_3O_3$ (338.11): C, 63.90; H, 5.06. Found: C, 63.85; H, 5.12%.



89ad
E/Z = 2.0:1

3-(3-Cyano-benzylidene)-2-methyl-4-oxo-cyclohex-1-enecarboxylic acid ethyl ester (89af): Prepared following the procedure **2a** and purified by column chromatography using EtOAc/hexane and isolated as a light yellow solid. Mp 52 °C; IR (neat): ν_{max} 2986, 2323, 1703 (C=O), 1671 (O-C=O), 1450, 1250, 1230, 1182, 1055, 685 cm^{-1}; ^{1}H NMR ($CDCl_3$, 10:1 ratio of *E/Z* isomers, major isomer) δ 7.64 (1H, m), 7.59-7.56 (2H, m), 7.42 (1H, t, *J* = 8.0 Hz), 6.91 (1H, s, olefinic-*H*), 4.28 (2H, q, *J* = 7.2 Hz, OCH_2CH_3), 2.87-2.82 (2H, m), 2.70 (2H, br t, *J* = 6.4 Hz), 2.25 (3H, t, *J* = 2.0 Hz, olefinic-CH_3), 1.35 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, 10:1 ratio of *E/Z* isomers, major isomer) δ 200.2 (C, C=O), 168. 3 (C, O-C=O), 139.6 (C), 138.2 (C), 137.2 (C), 133.5 (CH), 133.4 (CH), 132.7 (CH), 131.6 (CH), 130.1 (C), 128.8 (CH), 118.5 (C), 112.4 (C), 61.0 (CH_2, OCH_2CH_3), 39.3 (CH_2), 27.1 (CH_2), 16.5 (CH_3, olefinic-CH_3), 14.2 (CH_3, OCH_2CH_3); LRMS m/z 296.00 ($M + H^+$), calcd $C_{18}H_{17}NO_3$ 295.1208; HRMS m/z 318.1111 (M + Na), calcd for $C_{18}H_{17}NO_3Na$ 318.1106; Anal. calcd for $C_{18}H_{17}NO_3$ (295.12): C, 73.20; H, 5.80; N, 4.74. Found: C, 73.25; H, 5.76; N, 4.81%.

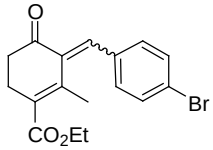
89af
E/Z = 10:1

2-Methyl-3-(3-nitro-benzylidene)-4-oxo-cyclohex-1-enecarboxylic acid ethyl ester (89ag): Prepared following the procedure **2a** and purified by column chromatography using EtOAc/hexane and isolated as a light yellow oily liquid. IR (neat): ν_{max} 2994, 2961, 1692 (C=O and O-C=O), 1527, 1440, 1352, 1306, 1280, 1241, 1185, 1056 cm^{-1}; ^{1}H NMR ($CDCl_3$, 1.5:1 ratio of *E/Z* isomers) δ 8.22-8.14 (4H, m), 7.69 (1H, d, *J* = 7.6 Hz), 7.64 (1H, d, *J* = 7.6 Hz), 7.63 (1H, s, olefinic-*H*), 7.57 (1H, t, *J* = 8.0 Hz), 7.49 (1H, t, *J* = 8.0 Hz), 6.99 (1H, s, olefinic-*H*), 4.29 (4H, q, *J* = 7.2 Hz, 2 x OCH_2CH_3), 2.88-2.83 (4H, m), 2.71 (2H, t, *J* = 6.4 Hz), 2.52 (2H, t, *J* = 6.4 Hz), 2.27 (3H, t, *J* = 2.0 Hz, olefinic-CH_3), 1.96 (3H, s, olefinic-CH_3), 1.36 (6H, t, *J* = 7.2 Hz, 2 x OCH_2CH_3); ^{13}C NMR ($CDCl_3$, 1.5:1 ratio of *E/Z* isomers) δ 201.1 (C, C=O), 200.2 (C, C=O), 168.3 (C, O-C=O), 167.0 (C, O-C=O), 148.2 (C), 148.0 (C), 141.8 (C), 139.7 (C), 139.5 (C),

89ag
E/Z = 1.5:1

138.3 (C), 137.6 (C), 137.1 (C), 135.3 (CH), 135.1 (CH), 133.5 (CH), 133.4 (CH), 132.0 (C), 130.3 (C), 129.4 (CH), 128.9 (CH), 124.3 (CH), 124.2 (CH), 123.7 (CH), 123.0 (CH), 61.1 (CH_2, O*C*H_2CH_3), 61.0 (CH_2, O*C*H_2CH_3), 39.3 (CH_2), 34.7 (CH_2), 27.1 (CH_2), 23.2 (CH_2), 20.4 (CH_3, olefinic-*C*H_3), 16.6 (CH_3, olefinic-*C*H_3), 14.3 (2 x CH_3, OCH_2*C*H_3); LRMS m/z 314.25 (M - H^+), calcd $C_{17}H_{17}NO_5$ 315.1107; HRMS m/z 338.1005 (M + Na), calcd for $C_{17}H_{17}NO_5Na$ 338.1005; Anal. calcd for $C_{17}H_{17}NO_5$ (315.11): C, 64.75; H, 5.43; N, 4.44. Found: C, 64.78; H, 5.39; N, 4.51%.

3-(4-Bromo-benzylidene)-2-methyl-4-oxo-cyclohex-1-enecarboxylic acid ethyl ester (89aj): Prepared following the procedure **2a** and purified by column chromatography using EtOAc/hexane and isolated as a yellow liquid. IR (neat): ν_{max} 1692 (C=O and O-C=O), 1594, 1270, 1242, 1196, 1055, 652 cm^{-1}; ^1H NMR ($CDCl_3$, 3:1 ratio of *E/Z* isomers) δ 7.56 (1H, s, olefinic-*H*), 7.50 (2H, br d, *J* = 8.4 Hz), 7.44 (2H, br d, *J* = 8.4 Hz), 7.28 (2H, br d, *J* = 8.4 Hz), 7.20 (2H, br d, *J* = 8.0 Hz), 6.88 (1H, s, olefinic-*H*), 4.28 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 4.27 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 2.86-2.78 (4H, m), 2.70 (2H, t, *J* = 6.4 Hz), 2.48 (2H, t, *J* = 6.4 Hz), 2.25 (3H, t, *J* = 2.0 Hz, olefinic-C*H*$_3$), 2.00 (3H, t, *J* = 1.2 Hz, olefinic-C*H*$_3$), 1.36 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$), 1.34 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, 3:1 ratio of *E*/*Z* isomers) δ 201.4 (C, C=O), 200.8 (C, C=O), 168.4 (C, O-C=O), 167.1 (C, O-C=O), 143.1 (C), 140.5 (C), 138.1 (C), 137.1 (C), 135.5 (CH), 135.0 (CH), 134.4 (C), 134.0 (C), 131.6 (2 x CH), 131.3 (2 x CH), 131.2 (2 x CH), 131.1 (2 x CH), 130.6 (C), 128.8 (C), 123.6 (C), 122.8 (C), 60.8 (CH_2, O*C*H_2CH_3), 60.7 (CH_2, O*C*H_2CH_3), 39.3 (CH_2), 34.8 (CH_2), 27.2 (CH_2), 23.1 (CH_2), 20.3 (CH_3, olefinic-*C*H_3), 16.6 (CH_3, olefinic-*C*H_3), 14.24 (CH_3, OCH_2*C*H_3), 14.19 (CH_3, OCH_2*C*H_3); LRMS m/z 349.00 (M + H^+), calcd $C_{17}H_{17}BrO_3$ 348.0361; Anal. calcd for $C_{17}H_{17}BrO_3$ (348.03): C, 58.47; H, 4.91. Found: C, 58.41; H, 4.95%.

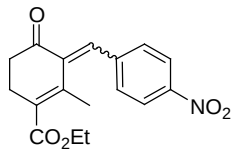


89aj
E/*Z* = 3:1

2b: Pyrrolidine-catalyzed Claisen-Schmidt and Michael reactions: In an ordinary glass vial equipped with a magnetic stirring bar, to 0.5 mmol of the

Hagemann's ester **88a** was added 1.0 mL of DMF solvent, and then the catalyst pyrrolidine **2a** (0.1 mmol, 8.33 µL) was added and then 0.5 mmol of aldehyde **28a-28q** was added in one-portion and the reaction mixture was stirred at 25 °C for the time indicated in Table 5. The crude reaction mixture was worked up with aqueous NH_4Cl solution and the aqueous layer was extracted with dichloromethane (2 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The pure products **89aa-aq** and **91** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

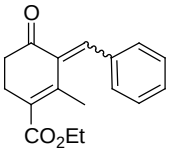
(*E*)-2-Methyl-3-(4-nitro-benzylidene)-4-oxo-cyclohex-1-enecarboxylic acid ethyl ester (89aa) and (*Z*)-2-Methyl-3-(4-nitro-benzylidene)-4-oxo-cyclohex-1-enecarboxylic acid ethyl ester (89aa): Prepared following the procedure **2b** and purified by column chromatography using EtOAc/hexane and isolated as a light yellow oil. IR (neat): ν_{max} 2932, 1709 (C=O and O-C=O), 1599, 1518, 1446, 1057, 898, 852, 738, 696 cm^{-1}; ^1H NMR ($CDCl_3$, 1.24:1 ratio of E/Z isomers) δ 8.23 (2H, d, *J* = 8.0 Hz), 8.17 (2H, d, *J* = 8.0 Hz), 7.63 (1H, s, olefinic-*H*, *E*-isomer), 7.49 (4H, d, *J* = 8.0 Hz), 6.98 (1H, s, olefinic-*H*, *Z*-isomer), 4.30 (4H, q, *J* = 7.2 Hz, 2 x $CO_2CH_2CH_3$), 2.85 (4H, m, CH_2), 2.72 (2H, t, *J* = 8.0 Hz, CH_2), 2.53 (2H, t, *J* = 8.0 Hz, CH_2), 2.26 (3H, s, olefinic-CH_3), 1.95 (3H, s, olefinic-CH_3), 1.37 (6H, t, *J* = 7.2 Hz, 2 x $CO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$, 1.24:1 ratio of E/Z isomers) δ 201.0 (C, C=O), 200.2 (C, C=O), 168.2 (C, O-C=O), 166.9 (C, O-C=O), 147.7 (C), 147.1 (C), 142.9 (C), 142.0 (C), 141.8 (C), 140.3 (C), 139.4 (C), 138.8 (C), 133.6 (CH), 133.4 (CH), 132.0 (C), 130.5 (C), 130.3 (2 x CH), 129.8 (2 x CH), 123.5 (2 x CH), 123.2 (2 x CH), 61.0 (CH_2, OCH_2CH_3), 60.99 (CH_2, OCH_2CH_3), 39.3 (CH_2), 34.5 (CH_2), 27.2 (CH_2), 23.2 (CH_2), 20.5 (CH_3, olefinic-CH_3), 16.5 (CH_3, olefinic-CH_3), 14.25 (CH_3), 14.21 (CH_3); HRMS (ESI-TOF) m/z 316.1172 ($M + H^+$), calcd $C_{17}H_{17}NO_5H^+$ 316.1186.



89aa
E/*Z* = 1.24:1

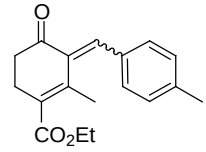
(*E*)-2-Methyl-3-(benzylidene)-4-oxo-cyclohex-1-enecarboxylic acid ethyl ester (89ab): Prepared following the procedure **2b** and purified by column chromatography

using EtOAc/hexane and isolated as a light yellow oil. IR (neat): ν_{max} 2980, 1697 (C=O and O-C=O), 1601, 1446, 1057, 758, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 5.3:1 ratio of E/Z isomers, Major isomer) δ 7.67 (1H, s, olefinic-*H*), 7.35 (5H, m, Ph-*H*), 4.27 (2H, q, *J* = 7.2 Hz, $CO_2CH_2CH_3$), 2.79 (2H, t, *J* = 5.2 Hz, CH_2), 2.48 (2H, t, *J* = 6.8 Hz, CH_2), 2.01 (3H, s, olefinic-CH_3), 1.36 (3H, t, *J* = 7.2 Hz, $CO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$, 5.3:1 ratio of E/Z isomers, Major isomer) δ 201.8 (C, C=O), 167.2 (C, O-C=O), 144.0 (C), 137.8 (C), 137.1 (CH), 135.1 (C), 129.9 (2 x CH), 129.5 (C), 129.3 (CH), 128.3 (2 x CH), 60.7 (CH_2, OCH_2CH_3), 34.98 (CH_2), 23.0 (CH_2), 20.4 (CH_3, olefinic-CH_3), 14.2 (CH_3, OCH_2CH_3); HRMS (ESI-TOF) m/z 293.1157 (M + Na^+), calcd $C_{17}H_{18}O_3Na^+$ 293.1156.



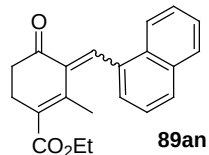
89ab
E/*Z* = 5.3:1

(*E*)-2-Methyl-3-(4-methyl-benzylidene)-4-oxo-cyclohex-1-enecarboxylic acid ethyl ester (89ac): Prepared following the procedure **2b** and purified by column chromatography using EtOAc/hexane and isolated as light yellow oil. IR (neat): ν_{max} 2978, 1701 (C=O and O-C=O), 1595, 1508, 1458, 1053, 814 cm^{-1}; ^1H NMR ($CDCl_3$, 5.5:1 ratio of E/Z isomers, Major isomer) δ 7.65 (1H, s, olefinic-*H*), 7.23 (2H, d, *J* = 8.0 Hz, Ph-*H*), 7.17 (2H, d, *J* = 8.0 Hz, Ph-*H*), 4.27 (2H, q, *J* = 7.2 Hz, $CO_2CH_2CH_3$), 2.78 (2H, t, *J* = 6.8 Hz, CH_2), 2.46 (2H, t, *J* = 6.8 Hz, CH_2), 2.37 (3H, s, Ar-CH_3), 2.03 (3H, s, olefinic-CH_3), 1.35 (3H, t, *J* = 7.2 Hz, $CO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$, 5.5:1 ratio of E/Z isomers, Major isomer) δ 201.8 (C, C=O), 167.2 (C, O-C=O), 144.3 (C), 139.8 (C), 137.3 (CH), 136.99 (C), 132.1 (C), 130.1 (2 x CH), 129.0 (2 x CH), 129.6 (C), 60.6 (CH_2, OCH_2CH_3), 35.0 (CH_2), 23.0 (CH_2), 21.4 (CH_3, Ar-CH_3), 20.3 (CH_3, olefinic-CH_3), 14.2 (CH_3, OCH_2CH_3); HRMS (ESI-TOF) m/z 285.1509 (M + H^+), calcd $C_{18}H_{20}O_3H^+$ 285.1491.



89ac
E/*Z* = 5.5:1

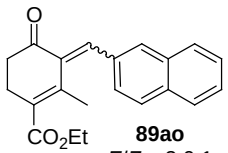
(*E*)-2-Methyl-3-(1-naphthalidene)-4-oxo-cyclohex-1-enecarboxylic acid ethyl ester (89an): Prepared following the procedure **2b** and purified by column chromatography using



89an
E/*Z* = 4.0:1

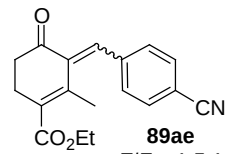
EtOAc/hexane and isolated as a light yellow oil. IR (neat): ν_{max} 2978, 1699 (C=O and O-C=O), 1597, 1506, 1444, 1057, 900, 862, 779, 733 cm^{-1}; ^1H NMR ($CDCl_3$, 4.0:1 ratio of E/Z isomers, Major isomer) δ 8.31 (1H, s), 8.01 (1H, m), 7.88 (2H, m), 7.57 (2H, m), 7.44 (1H, m), 7.31 (1H, br d, *J* = 7.2 Hz), 4.25 (2H, q, *J* = 7.2 Hz, $CO_2CH_2CH_3$), 2.85 (2H, br t, *J* = 6.8 Hz, CH_2), 2.57 (2H, t, *J* = 6.8 Hz, CH_2), 1.79 (3H, s, olefinic-CH_3), 1.33 (3H, t, *J* = 7.2 Hz, $CO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$, 4.0:1 ratio of E/Z isomers, Major isomer) δ 201.0 (C, C=O), 167.3 (C, O-C=O), 143.6 (C), 138.8 (C), 135.9 (CH), 133.2 (C), 133.0 (C), 131.3 (C), 130.0 (C), 129.7 (CH), 128.5 (CH), 127.3 (CH), 126.6 (CH), 126.3 (CH), 125.0 (CH), 124.6 (CH), 60.6 (CH_2, OCH_2CH_3), 35.4 (CH_2), 23.2 (CH_2), 20.1 (CH_3, olefinic-CH_3), 14.2 (CH_3, OCH_2CH_3); HRMS (ESI-TOF) m/z 343.1331 (M + Na^+), calcd $C_{21}H_{20}O_3Na^+$ 343.1312.

(*E*)-2-Methyl-3-(2-naphthalidene)-4-oxo-cyclohex-1-enecarboxylic acid ethyl ester (89ao): Prepared following the procedure **2b** and purified by column chromatography using EtOAc/hexane and isolated as a light yellow oil. IR (neat): ν_{max} 3055, 2978, 1701 (C=O and O-C=O), 1601, 1504, 1452, 1057, 912, 858, 750 cm^{-1}; ^1H NMR ($CDCl_3$, 3.0:1 ratio of E/Z isomers, Major isomer) δ 7.83-7.40 (8H, m, Ph-*H*), 4.29 (2H, q, *J* = 7.2 Hz, $CO_2CH_2CH_3$), 2.84 (2H, m, CH_2), 2.50 (2H, m, CH_2), 2.03 (3H, s, olefinic-CH_3), 1.26 (3H, t, *J* = 7.2 Hz, $CO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$, 3.0:1 ratio of E/Z isomers, Major isomer) δ 201.7 (C, C=O), 167.2 (C, O-C=O), 143.9 (C), 137.8 (C), 137.1 (CH), 133.4 (C), 132.8 (C), 132.6 (C), 130.2 (CH), 130.1 (C), 128.3 (CH), 127.8 (CH), 127.7 (CH), 127.1 (CH), 126.8 (CH), 126.6 (CH), 60.6 (CH_2, OCH_2CH_3), 34.9 (CH_2), 23.1 (CH_2), 20.5 (CH_3, olefinic-CH_3), 14.2 (CH_3, OCH_2CH_3); HRMS (ESI-TOF) m/z 343.1331 (M + Na^+), calcd $C_{21}H_{20}O_3Na^+$ 343.1312.



89ao
E/*Z* = 3.0:1

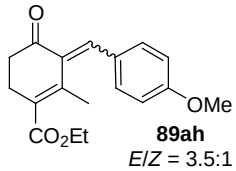
(*E*)-2-Methyl-3-(4-cyano-benzylidene)-4-oxo-cyclohex-1-enecarboxylic acid ethyl ester (89ae) and (*Z*)-2-Methyl-3-(4-cyano-benzylidene)-4-oxo-cyclohex-1-enecarboxylic acid ethyl ester (89ae): Prepared



89ae
E/*Z* = 1.5:1

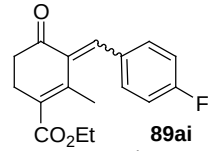
following the procedure **2b** and purified by column chromatography using EtOAc/hexane and isolated as a light yellow oil. IR (neat): ν_{max} 2984, 1701 (C=O and O-C=O), 1602, 1442, 1055, 839, 750 cm^{-1}; ^1H NMR ($CDCl_3$, 1.5:1 ratio of E/Z isomers) δ 7.67 (4H, d, *J* = 8.4 Hz), 7.61 (1H, br s, olefinic-*H*), 7.44 (4H, m, Ph-*H*), 6.95 (1H, s, olefinic-*H*), 4.30 (4H, q, *J* = 7.2 Hz, $CO_2CH_2CH_3$), 2.88 (4H, m, CH_2), 2.71 (2H, t, *J* = 6.8 Hz, CH_2), 2.51 (2H, t, *J* = 6.8 Hz), 2.25 (3H, s, olefinic-CH_3), 2.03 (3H, s, olefinic-CH_3), 1.36 (6H, t, *J* = 7.2 Hz, 2 x $CO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$, 1.5:1 ratio of E/Z isomers) δ 201.0 (C, C=O), 200.3 (C, C=O), 168.1 (C, O-C=O), 166.8 (C, O-C=O), 142.0 (C), 140.7 (C), 139.9 (C), 139.8 (C), 139.4 (C), 138.4 (C), 134.0 (CH), 133.8 (CH), 131.9 (2 x CH), 131.6 (2 x CH), 130.1 (2 x CH), 130.0 (C), 129.6 (2 x CH), 128.3 (C), 118.7 (C), 118.2 (C), 112.4 (C), 111.4 (C), 60.9 (CH_2, OCH_2CH_3), 60.8 (CH_2, OCH_2CH_3), 39.2 (CH_2), 34.5 (CH_2), 27.1 (CH_2), 23.0 (CH_2), 20.4 (CH_3, olefinic-CH_3), 16.4 (CH_3, olefinic-CH_3), 14.2 (CH_3, OCH_2CH_3), 14.1 (CH_3, OCH_2CH_3).

(*E*)-2-Methyl-3-(4-methoxy-benzylidene)-4-oxo-cyclohex-1-enecarboxylic acid ethyl ester (89ah): Prepared following the procedure **2b** and purified by column chromatography using EtOAc/hexane and isolated as a light yellow oil. ^1H NMR ($CDCl_3$, 3.5:1 ratio of E/Z isomers, Major isomer) δ 7.63 (1H, s, olefinic-*H*), 7.29 (2H, d, *J* = 8.4 Hz, Ph-*H*), 6.89 (2H, d, *J* = 8.4 Hz, Ph-*H*), 4.28 (2H, q, *J* = 6.8 Hz, $CO_2CH_2CH_3$), 3.84 (3H, s, OCH_3), 2.78 (2H, br s, CH_2), 2.45 (2H, t, *J* = 6.8 Hz, CH_2), 2.07 (3H, s, olefinic-CH_3), 1.36 (3H, t, *J* = 6.8 Hz, $CO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$, 3.5:1 ratio of E/Z isomers, Major isomer) δ 201.9 (C, C=O), 167.2 (C, O-C=O), 160.7 (C), 144.6 (C), 137.0 (CH), 135.9 (C), 132.1 (2 x CH), 129.3 (C), 127.3 (C), 113.5 (2 x CH), 60.6 (CH_2, OCH_2CH_3), 55.3 (CH_3, OCH_3), 35.1 (CH_2), 23.0 (CH_2), 20.3 (CH_3, olefinic-CH_3), 14.3 (CH_3, OCH_2CH_3).



89ah
E/*Z* = 3.5:1

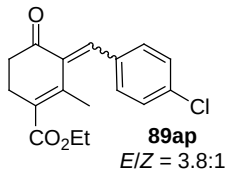
(*E*)-2-Methyl-3-(4-Fluoro-benzylidene)-4-oxo-cyclohex-1-enecarboxylic acid ethyl ester (89ai): Prepared following the procedure **2b** and purified by



89ai
E/*Z* = 3.5:1

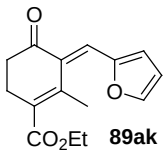
column chromatography using EtOAc/hexane and isolated as a light yellow oil. IR (neat): ν_{max} 2972, 1695 (C=O and O-C=O), 1595, 1504 cm^{-1}; ^1H NMR ($CDCl_3$, 3.5:1 ratio of E/Z isomers, Major isomer) δ 7.61 (1H, s, olefinic-*H*), 7.32 (2H, d, *J* = 5.6 Hz, Ph-*H*), 7.08 (2H, d, *J* = 5.6 Hz, Ph-*H*), 4.29 (2H, q, *J* = 6.8 Hz, $CO_2CH_2CH_3$), 2.79 (2H, br s, CH_2), 2.48 (2H, t, *J* = 6.8 Hz, CH_2), 2.01 (3H, s, olefinic-CH_3), 1.36 (3H, t, *J* = 6.8 Hz, $CO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$, 3.5:1 ratio of E/Z isomers, Major isomer) δ 201.6 (C, C=O), 167.1 (C, O-C=O), 161.9 (C), 143.5 (C), 137.6 (C), 135.7 (CH), 131.9 (CH), 131.8 (CH), 131.1 (C), 130.3 (C), 115.6 (CH), 115.4 (CH), 60.7 (CH_2, OCH_2CH_3), 34.9 (CH_2), 23.0 (CH_2), 20.3 (CH_3, olefinic-CH_3), 14.2 (CH_3, OCH_2CH_3); HRMS (ESI-TOF) m/z 289.1228 ($M + H^+$), calcd $C_{17}H_{17}FO_3H^+$ 289.1240.

(*E*)-2-Methyl-3-(4-Chloro-benzylidene)-4-oxo-cyclohex-1-enecarboxylic acid ethyl ester (89ap): Prepared following the procedure **2b** and purified by column chromatography using EtOAc/hexane and isolated as a light yellow oil. IR (neat): ν_{max} 2978, 1697 (C=O and O-C=O), 1593, 1485, 1442, 1053, 900, 831, 744 cm^{-1}; ^1H NMR ($CDCl_3$, 3.8:1 ratio of E/Z isomers, Major isomer) δ 7.59 (1H, s, olefinic-*H*), 7.34 (2H, d, *J* = 8.4 Hz, Ph-*H*), 7.26 (2H, d, *J* = 8.4 Hz, Ph-*H*), 4.28 (2H, q, *J* = 6.8 Hz, $CO_2CH_2CH_3$), 2.81 (2H, t, *J* = 6.0 Hz, CH_2), 2.48 (2H, t, *J* = 6.0 Hz, CH_2), 2.00 (3H, s, olefinic-CH_3), 1.36 (3H, t, *J* = 6.8 Hz, $CO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$, 3.8:1 ratio of E/Z isomers, Major isomer) δ 201.4 (C, C=O), 167.1 (C, O-C=O), 143.2 (C), 138.0 (C), 135.4 (CH), 134.9 (C), 133.5 (C), 131.1 (2 x CH), 130.6 (C), 128.6 (2 x CH), 60.8 (CH_2, OCH_2CH_3), 34.8 (CH_2), 23.0 (CH_2), 20.3 (CH_3, olefinic-CH_3), 14.2 (CH_3, OCH_2CH_3); HRMS (ESI-TOF) m/z 327.0768 ($M + Na^+$), calcd $C_{17}H_{17}ClO_3Na^+$ 327.0766.



89ap
E/*Z* = 3.8:1

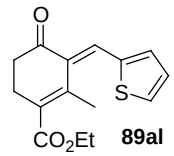
(*E*)-2-Methyl-3-(Furan-2-ylmethylene)-4-oxo-cyclohex-1-enecarboxylic acid ethyl ester (89ak): Prepared following the procedure **2b** and purified by column chromatography using EtOAc/hexane and isolated as a light yellow oil. IR (neat): ν_{max} 2980, 1699 (C=O and O-C=O), 1572, 1466, 1093, 1057, 887, 846, 756 cm^{-1}; ^1H NMR ($CDCl_3$, 99:1 ratio of E/Z isomers) δ 7.79 (1H, s, olefinic-*H*), 7.53 (1H, br s), 6.99 (1H, br s), 6.51 (1H, br s), 4.26 (2H, q, *J* = 6.8



89ak

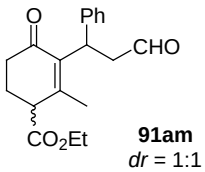
Hz, $CO_2CH_2CH_3$), 2.78 (2H, t, *J* = 6.4 Hz, CH_2), 2.64 (2H, t, *J* = 6.4 Hz, CH_2), 2.28 (3H, s, olefinic-CH_3), 1.32 (3H, t, *J* = 6.8 Hz, $CO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$, 99:1 ratio of E/Z isomers) δ 198.9 (C, C=O), 168.5 (C, O-C=O), 151.7 (C), 145.1 (CH), 141.5 (C), 130.9 (C), 127.8 (C), 124.1 (CH), 118.2 (CH), 113.1 (CH), 60.7 (CH_2, OCH_2CH_3), 38.8 (CH_2), 25.9 (CH_2), 16.7 (CH_3, olefinic-CH_3), 14.2 (CH_3, OCH_2CH_3).

(*E*)-2-Methyl-3-(Thiophen-2-ylmethylene)-4-oxo-cyclohex-1-enecarboxylic acid ethyl ester (89al): Prepared following the procedure **2b** and purified by column chromatography using EtOAc/hexane and isolated as a light yellow oil. IR (neat): ν_{max} 2968, 1697 (C=O and O-C=O), 1454, 1242, 904, 709 cm^{-1}; ^{1}H NMR ($CDCl_3$, 99:1 ratio of E/Z isomers) δ 7.53 (1H, d, *J* = 4.8 Hz), 7.48 (1H, d, *J* = 3.6 Hz), 7.27 (1H, s, olefinic-*H*), 7.10 (1H, dd, *J* = 4.8, 3.6 Hz), 4.27 (2H, q, *J* = 7.2 Hz, $CO_2CH_2CH_3$), 2.76 (2H, t, *J* = 6.4 Hz, CH_2), 2.64 (2H, t, *J* = 6.4 Hz, CH_2), 2.32 (3H, s, olefinic-CH_3), 1.33 (3H, t, *J* = 7.2 Hz, $CO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$, 99:1 ratio of E/Z isomers) δ 199.6 (C, C=O), 168.5 (C, O-C=O), 141.7 (C), 138.5 (CH), 138.4 (C), 133.2 (CH), 131.7 (CH), 129.2 (C), 127.2 (C), 126.9 (CH), 60.6 (CH_2, OCH_2CH_3), 38.4 (CH_2), 25.3 (CH_2), 16.7 (CH_3, olefinic-CH_3), 14.2 (CH_3, OCH_2CH_3).



89al

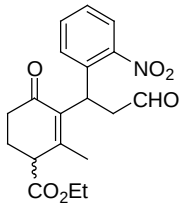
2-Methyl-4-oxo-3-(3-oxo-1-phenyl-propyl)-cyclohex-2-enecarboxylic acid ethyl ester (91am): Prepared following the procedure **2b** and purified by column chromatography using EtOAc/hexane and isolated as an oil. IR (neat): ν_{max} 2980, 2727, 1728 (C=O), 1666 (O-C=O), 1190, 1028, 860, 756 cm^{-1}; ^{1}H NMR ($CDCl_3$, 1:1 mixture of diastereomers) δ 9.76 (2H, s, *H*-C=O), 7.22 (10H, m, Ph-*H*), 4.76 (1H, t, *J* = 6.8 Hz), 4.66 (1H, t, *J* = 6.8 Hz), 4.18 (4H, q, *J* = 7.2 Hz, 2 x $CO_2CH_2CH_3$), 3.25 (5H, m), 2.56-2.15 (9H, m), 2.06 (3H, s, olefinic-CH_3), 2.03 (3H, s, olefinic-CH_3), 1.25 (6H, t, *J* = 7.2 Hz, 2 x $CO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$, 1:1 mixture of diastereomers) δ 201.2 (C, C=O), 201.1 (C, C=O), 197.2 (C, C=O), 197.1 (C, C=O), 171.7 (C, O=C-O), 171.6 (C, O=C-O), 152.8 (C), 152.6 (C), 141.9 (C), 141.8 (C), 138.5 (C), 138.2 (C), 128.3 (2 x CH), 128.2 (2 x CH),



91am
dr = 1:1

127.3 (2 x CH), 127.1 (2 x CH), 126.1 (CH), 126.07 (CH), 61.26 (CH_2), 61.25 (CH_2), 48.51 (CH), 48.50 (CH), 46.8 (CH), 46.6 (CH), 36.4 (CH_2), 36.2 (CH_2), 35.3 (CH2), 35.2 (CH2), 25.4 (CH_2), 25.2 (CH_2), 21.3 (CH_3), 21.2 (CH_3), 14.1 (CH_3), 14.0 (CH_3).

2-Methyl-3-[1-(2-nitro-phenyl)-3-oxo-propyl]-4-oxo-cyclohex-2-enecarboxylic acid ethyl ester (91aq): Prepared following the procedure **2b** and purified by column chromatography using EtOAc/hexane and isolated as a light yellow oily liquid. IR (neat): ν_{max} 2980, 2930, 2728, 1730 (C=O), 1665 (O-C=O), 1532, 1368, 743 cm^{-1}; ^1H NMR ($CDCl_3$, 1.2:1 ratio of diastereomers) δ 9.80 (1H, s, *H*-C=O), 9.72 (1H, s, *H*-C=O), 7.71 (1H, d, *J* = 8.4 Hz), 7.59 (1H, d, *J* = 8.0 Hz), 7.55-7.48 (4H, m), 7.36-7.30 (2H, m), 5.10 (2H, t, *J* = 6.8 Hz), 4.18 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 4.14 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 3.47-3.35 (2H, m), 3.30 (1H, t, *J* = 4.4 Hz), 3.27 (1H, t, *J* = 4.4 Hz), 3.21-3.09 (2H, m), 2.54-2.46 (1H, m), 2.42-2.35 (2H, m), 2.25-2.17 (4H, m), 2.11-2.06 (1H, m), 2.04 (3H, s, olefinic-C*H*$_3$), 1.83 (3H, s, olefinic-C*H*$_3$), 1.27 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$), 1.22 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, 1.2:1 ratio of diastereomers) δ 200.4 (C, H-C=O), 200.3 (C, H-C=O), 198.1 (C, C=O), 197.2 (C, C=O), 171.45 (C, O-C=O), 171.42 (C, O-C=O), 154.8 (C), 154.3 (C), 149.8 (C), 149.4 (C), 136.5 (C), 136.1 (2 x C), 134.8 (C), 132.6 (CH), 131.9 (CH), 130.3 (CH), 130.0 (CH), 127.4 (CH), 127.2 (CH), 124.2 (CH), 123.8 (CH), 61.5 (CH_2, O*C*H$_2$CH$_3$), 61.4 (CH_2, O*C*H$_2$CH$_3$), 48.4 (CH), 48.1 (CH), 46.6 (CH_2), 45.7 (CH_2), 34.9 (CH_2), 34.8 (CH_2), 33.4 (CH), 33.0 (CH), 25.0 (CH_2), 24.9 (CH_2), 21.4 (CH_3, olefinic-*C*H$_3$), 21.0 (CH_3, olefinic-*C*H$_3$), 14.1 (CH_3, OCH$_2$*C*H$_3$), 14.0 (CH_3, OCH$_2$*C*H$_3$); LRMS m/z 360.05 (M + H^+), calcd $C_{19}H_{21}NO_6$ 359.1369; HRMS m/z 382.1268 (M + Na), calcd for $C_{19}H_{21}NO_6Na$ 382.1267; Anal. calcd for $C_{19}H_{21}NO_6$ (359.13): C, 63.50; H, 5.89; N, 3.90. Found: C, 63.41; H, 5.93; N, 3.95%.

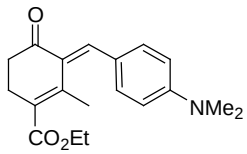


91aq
dr = 1.2:1

2c: (*S*)-1-(2-Pyrrolidinylmethyl)pyrrolidine-catalyzed Claisen-Schmidt reactions: In an ordinary glass vial equipped with a magnetic stirring bar, to 0.5 mmol of the Hagemann's ester **88a** was added 1.0 mL of DMF solvent, and then the catalyst

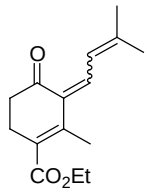
(*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine **2i** (0.1 mmol, 16.3 µL) was added and then 0.5 mmol of aldehyde **28b-2s & 45d** was added in one-portion and the reaction mixture was stirred at 25 °C for the time indicated in Table 6. The crude reaction mixture was worked up with aqueous NH_4Cl solution and the aqueous layer was extracted with dichloromethane (2 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The pure products **89ab-as** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

3-(4-Dimethylamino-benzylidene)-2-methyl-4-oxo-cyclohex-1-enecarboxylic acid ethyl ester (89ar): Prepared following the procedure **2c** and purified by column chromatography using EtOAc/hexane and isolated as a yellow liquid. IR (neat): ν_{max} 2926, 2855, 1705 (C=O), 1678 (O-C=O), 1595, 1522, 1370, 1055, 808 cm^{-1}; ^1H NMR ($CDCl_3$, 99:1 ratio of *E/Z* isomers) δ 7.66 (1H, s, olefinic-*H*), 7.26 (2H, d, *J* = 8.8 Hz), 6.65 (2H, d, *J* = 8.8 Hz), 4.27 (2H, q, *J* = 7.2 Hz, OCH_2CH_3), 3.03 (6H, s, $N(CH_3)_2$), 2.76 (2H, t, *J* = 6.0 Hz), 2.43 (2H, t, *J* = 6.4 Hz), 2.16 (3H, s, olefinic-CH_3), 1.36 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, 99:1 ratio of *E/Z* isomers) δ 202.0 (C, C=O), 167.4 (C, O-C=O), 151.2 (C), 145.9 (C), 138.4 (CH), 133.3 (C), 132.8 (2 x CH), 128.0 (C), 122.0 (C), 111.2 (2 x CH), 60.4 (CH_2, OCH_2CH_3), 40.0 (2 x CH_3, $N(CH_3)_2$), 35.5 (CH_2), 23.0 (CH_2), 20.5 (CH_3, olefinic-CH_3), 14.4 (CH_3, OCH_2CH_3); LRMS m/z 314.25 ($M + H^+$), calcd $C_{19}H_{23}NO_3$ 313.1678; Anal. calcd for $C_{19}H_{23}NO_3$ (313.16): C, 72.82; H, 7.40; N, 4.47. Found: C, 72.91; H, 7.35; N, 4.56%.



89ar
E/Z = 99:1

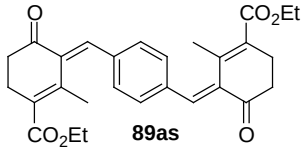
2-Methyl-3-(3-methyl-but-2-enylidene)-4-oxo-cyclohex-1-enecarboxylic acid ethyl ester (89ad): Prepared following the procedure **2c** and purified by column chromatography using EtOAc/hexane and isolated as a red colored liquid. IR (neat): ν_{max} 2978, 2930, 1713 (C=O), 1684 (O-C=O), 1597, 1447,



89ad
E/Z = 1:5

1372, 1246 cm^{-1}; ^1H NMR ($CDCl_3$, 1:5 ratio of *E/Z* isomers, major isomer) δ 7.53 (1H, d, *J* = 12.8 Hz), 6.29 (1H, d, *J* = 12.8 Hz), 4.26 (2H, q, *J* = 7.2 Hz, OCH_2CH_3), 2.66 (2H, br t, *J* = 6.4 Hz), 2.43 (2H, t, *J* = 6.4 Hz), 2.38 (3H, s, olefinic-CH_3), 1.98 (3H, s), 1.96 (3H, s), 1.34 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, 1:5 ratio of *E/Z* isomers, major isomer) δ 201.5 (C, C=O), 167.7 (C, O-C=O), 150.9 (C), 143.9 (C), 133.5 (C), 133.2 (CH), 128.1 (C), 122.3 (CH), 60.5 (CH_2, OCH_2CH_3), 35.9 (CH_2), 27.6 (CH_3), 23.1 (CH_2), 21.6 (CH_3), 18.9 (CH_3, olefinic CH_3), 14.3 (CH_3, OCH_2CH_3); LRMS m/z 249.15 ($M + H^+$), calcd $C_{15}H_{20}O_3$ 248.1412; Anal. calcd for $C_{15}H_{20}O_3$ (248.14): C, 72.55; H, 8.12. Found: C, 72.61; H, 8.08%.

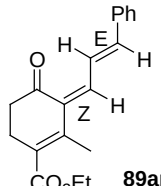
(*E, E*)-bis-1,4-[2-Methyl-3-methylidenyl-4-oxo-cyclohex-1-enecarboxylic acid ethyl ester]-benzene (89as): Prepared following the procedure **2c** and purified by column chromatography using EtOAc/hexane and isolated as a light yellow solid and it has a C_2 symmetry.



89as

IR (neat): ν_{max} 2970, 1701 (C=O and O-C=O), 1577, 1377, 1051, 831 cm^{-1}; ^1H NMR ($CDCl_3$, 99:1 ratio of E/Z isomers) δ 7.63 (2H, s, olefinic-*H*), 7.34 (4H, s, Ph-*H*), 4.29 (2H, q, *J* = 6.8 Hz, $CO_2CH_2CH_3$), 2.82 (4H, m, CH_2), 2.48 (4H, t, *J* = 6.0 Hz, CH_2), 2.02 (3H, s, olefinic-CH_3), 1.36 (3H, t, *J* = 6.8 Hz, $CO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$, 99:1 ratio of E/Z isomers) δ 201.6 (C, C=O), 167.1 (C, O-C=O), 143.4 (C), 138.5 (C), 136.2 (C), 135.9 (CH), 130.6 (C), 129.9 (4 x CH), 60.8 (CH_2, OCH_2CH_3), 34.8 (CH_2), 23.1 (CH_2), 20.4 (CH_3, olefinic-CH_3), 14.3 (CH_3, OCH_2CH_3); GCMS: m/z 462.20 (M^+), calcd $C_{28}H_{30}O_6$ 462.2042.; base peak: m/z 416.15 (M-EtOH).

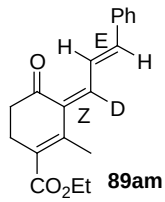
(*E, Z, E*)-2-Methyl-4-oxo-3-(3-phenyl-allylidene)-cyclohex-1-enecarboxylic acid ethyl ester (89am): Prepared following the procedure **2c** and purified by column chromatography using EtOAc/hexane and isolated as a light yellow solid. IR (neat): ν_{max} 3078, 2980, 1693, 1572, 1552, 1446, 1055, 837, 752, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 1:6 ratio of *E/Z* isomers, major isomer) δ 8.21 (1H, dd, *J* = 15.6, 11.6 Hz), 7.54-7.52 (2H, m), 7.37-7.28 (3H, m), 6.96 (1H, d, *J* = 15.6 Hz), 6.83 (1H, d, *J* = 11.6 Hz), 4.24 (2H, q, *J* = 7.2 Hz,



89am
E/Z = 1:6

$CO_2CH_2CH_3$), 2.77 (2H, br t, J = 6.0 Hz, CH_2), 2.62 (2H, dt, J = 6.8, 0.8 Hz, CH_2), 2.26 (3H, t, J = 1.6 Hz, olefinic-CH_3), 1.34 (3H, t, J = 7.2 Hz, $CO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$, 1:6 ratio of *E/Z* isomers, major isomer) δ 200.6 (C, C=O), 168.6 (C, O-C=O), 143.7 (CH), 141.4 (C), 138.5 (CH), 136.5 (C), 132.6 (C), 129.1 (CH), 128.7 (2 x CH), 127.6 (2 x CH), 127.5 (C), 126.4 (CH), 60.6 (CH_2), 39.3 (CH_2), 25.8 (CH_2), 16.4 (CH_3), 14.2 (CH_3); HRMS (ESI-TOF) m/z 319.1294 (M + Na^+), calcd $C_{19}H_{20}O_3$+Na 319.1305.

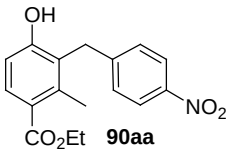
(*E*, *Z*, *E*)-2-Methyl-4-oxo-3-[1-deutero-3-phenyl-allylidene]-cyclohex-1-enecarboxylic acid ethyl ester (89am): Prepared following the procedure **2c** and purified by column chromatography using EtOAc/hexane and isolated as a light yellow solid. ^{1}H NMR ($CDCl_3$) δ 8.20 (1H, d, J = 16.0 Hz), 7.53(2H, br d, J = 7.2 Hz, Ph-*H*), 7.37-7.28 (3H, m, Ph-*H*), 6.95 (1H, d, J = 15.6 Hz), 4.25 (2H, q, J = 7.2 Hz, $CO_2CH_2CH_3$), 2.77 (2H, br t, J = 6.0 Hz, CH_2), 2.61 (2H, t, J = 6.8 Hz, CH_2), 2.25 (3H, t, J = 1.6 Hz, olefinic-CH_3), 1.33 (3H, t, J = 6.8 Hz, $CO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$) δ 200.6 (C, C=O), 168.5 (C, O-C=O), 143.7 (CH), 141.3 (C), 136.5 (C), 132.5 (C), 129.1 (CH), 128.7 (2 x CH), 127.6 (2 x CH), 127.4 (C), 126.3 (CH), 60.6 (CH_2), 39.2 (CH_2), 25.8 (CH_2), 16.3 (CH_3), 14.2 (CH_3).



89am

2d: (*S*)-1-(2-Pyrrolidinylmethyl)pyrrolidine-catalyzed cascade Claisen-Schmidt and iso-aromatization reactions: In an ordinary glass vial equipped with a magnetic stirring bar, to 0.5 mmol of the Hagemann's esters **88a-s** was added 1.0 mL of DMSO solvent, and then the catalyst (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine **2i** (0.1 mmol, 16.3 µL) was added and then 0.5 mmol of aldehydes **28a-u** was added in one-portion and the reaction mixture was stirred at 25 °C for the time indicated in Table 7. The crude reaction mixture was worked up with aqueous NH_4Cl solution and the aqueous layer was extracted with dichloromethane (2 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The pure cascade products **90** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

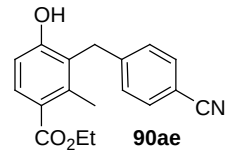
4-Hydroxy-2-methyl-3-(4-nitrobenzyl)-benzoic acid ethyl ester (90aa): Prepared following the procedure **2d** and purified by column chromatography using EtOAc/hexane and isolated as a white solid.



90aa

IR (neat): ν_{max} 3339 (O-H), 2985, 1678 (O-C=O), 1595, 1578, 1519, 1345, 1292, 1263, 1174, 1153, 1108, 1049, 1007, 774, 749, 732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.05 (2H, td, *J* = 8.8, 2.0 Hz), 7.71 (1H, d, *J* = 8.8 Hz), 7.25 (2H, d, *J* = 8.8 Hz), 6.76 (1H, d, *J* = 8.8 Hz) [Ar-*H*]; 6.24 (1H, s, O-*H*), 4.32 (2H, q, *J* = 7.2 Hz, $CO_2CH_2CH_3$), 4.19 (2H, s, -CH_2Ar), 2.44 (3H, s, olefinic-CH_3), 1.37 (3H, t, *J* = 6.8 Hz, $CO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$) δ 168.3 (C, O-C=O), 156.9 (C), 148.1 (C), 146.2 (C), 141.0 (C), 130.9 (CH), 128.8 (2 x CH), 125.2 (C), 123.8 (C), 123.6 (2 x CH), 112.5 (CH), 60.8 (CH_2, OCH_2CH_3), 31.7 (CH_2), 17.0 (CH_3), 14.3 (CH_3); HRMS (ESI-TOF) m/z 316.1180 ($M + H^+$), calcd for $C_{17}H_{17}O_5NH^+$ 316.1179.

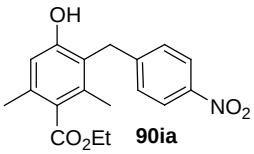
4-Hydroxy-2-methyl-3-(4-cyanobenzyl)-benzoic acid ethyl ester (90ae): Prepared following the procedure **2d** and purified by column chromatography using EtOAc/hexane and isolated as a white solid.



90ae

IR (neat): ν_{max} 3335 (O-H), 2989, 1682 (O-C=O), 1579, 1267, 1153, 1049, 1006, 779, 756 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.71 (1H, d, *J* = 8.4 Hz), 7.49 (2H, d, *J* = 8.4 Hz), 7.22 (2H, d, *J* = 8.4 Hz), 6.78 (1H, d, *J* = 8.4 Hz) [Ar-*H*]; 6.10 (1H, s, O-*H*), 4.32 (2H, q, *J* = 6.8 Hz, $CO_2CH_2CH_3$), 4.16 (2H, s, -CH_2Ar), 2.42 (3H, s, olefinic-CH_3), 1.36 (3H, t, *J* = 6.8 Hz, $CO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$) δ 168.6 (C, O-C=O), 157.6 (C), 146.3 (C), 140.9 (C), 132.0 (2 x CH), 130.8 (CH), 128.9 (2 x CH), 125.2 (C), 123.1 (C), 118.9 (C), 112.4 (CH), 109.0 (C), 60.8 (CH_2, OCH_2CH_3), 31.8 (CH_2, CH_2Ar), 16.97 (CH_3, olefinic-CH_3), 14.2 (CH_3); GCMS m/z 295.12 (M^+), calcd for $C_{18}H_{17}O_3N$ 295.1208.

4-Hydroxy-2, 6-dimethyl-3-(4-nitrobenzyl)-benzoic acid ethyl ester (90ia): Prepared following the procedure **2d** and purified by column chromatography using EtOAc/hexane and isolated as a light yellow solid.

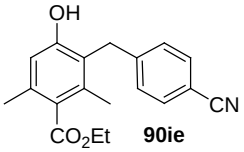


90ia

IR (neat): ν_{max} 3385 (O-H), 2976, 1716 (O-C=O), 1651, 1601, 1518, 1344, 1151, 1051, 734 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.06 (2H, dd, *J* =

8.8, 2.0 Hz), 7.28 (2H, br d, *J* = 8.8 Hz), 6.54 (1H, s) [Ar-*H*]; 6.07 (1H, s, O-*H*), 4.37 (2H, q, *J* = 7.2 Hz, $CO_2CH_2CH_3$), 4.11 (2H, s, -CH_2Ar), 2.25 (3H, s, olefinic-CH_3), 2.16 (3H, s, olefinic-CH_3), 1.37 (3H, t, *J* = 7.2 Hz, $CO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$) δ 170.6 (C, O-C=O), 154.6 (C), 148.3 (C), 146.2 (C), 135.6 (C), 134.9 (C), 128.9 (2 x CH), 127.8 (C), 123.5 (2 x CH), 121.9 (C), 114.6 (CH), 61.1 (CH_2, OCH_2CH_3), 31.5 (CH_2, CH_2Ar), 19.6 (CH_3, olefinic-CH_3), 16.8 (CH_3, olefinic-CH_3), 14.2 (CH_3).

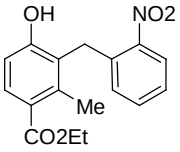
4-Hydroxy-2, 6-dimethyl-3-(4-cyanobenzyl)-benzoic acid ethyl ester (90ie):



90ie

Prepared following the procedure **2d** and purified by column chromatography using EtOAc/hexane and isolated as a white solid. IR (neat): ν_{max} 3398 (O-H), 2986, 1718 (O-C=O), 1604, 1504, 1051, 852, 615 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.49 (2H, d, *J* = 8.4 Hz), 7.22 (2H, d, *J* = 8.4 Hz), 6.53 (1H, s) [Ar-*H*]; 6.07 (1H, s, O-*H*), 4.36 (2H, q, *J* = 7.2 Hz, $CO_2CH_2CH_3$), 4.07 (2H, s, -CH_2Ar), 2.24 (3H, s, olefinic-CH_3), 2.14 (3H, s, olefinic-CH_3), 1.37 (3H, t, *J* = 7.2 Hz, $CO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$) δ 170.6 (C, O-C=O), 154.6 (C), 146.1 (C), 135.6 (C), 134.9 (C), 132.1 (2 x CH), 128.9 (2 x CH), 127.7 (C), 121.9 (C), 119.1 (C), 114.6 (CH), 109.4 (C), 61.0 (CH_2, OCH_2CH_3), 31.7 (CH_2, CH_2Ar), 19.6 (CH_3, olefinic-CH_3), 16.8 (CH_3, olefinic-CH_3), 14.2 (CH_3).

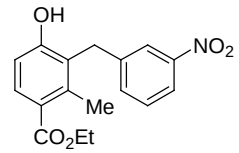
4-Hydroxy-2-methyl-3-(2-nitro-benzyl)-benzoic acid ethyl ester (90at): Prepared following the procedure **2d** and purified by column chromatography using EtOAc/hexane and isolated as a yellow solid. Mp 122 °C; IR (neat): ν_{max} 3369 (O-*H*), 1691 (O-C=O), 1585, 1524, 1352, 1295, 1265 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.93 (1H, dd, *J* = 8.0, 1.6 Hz), 7.74 (1H, d, *J* = 8.4 Hz), 7.36 (1H, dt, *J* = 7.6, 1.6 Hz), 7.30 (1H, dt, *J* = 7.6, 1.2 Hz), 6.84 (1H, br d, *J* = 7.6 Hz); 6.79 (1H, br s, O-*H*), 6.75 (1H, d, *J* = 8.8 Hz), 4.38 (2H, s, CH_2Ar), 4.32 (2H, q, *J* = 7.2 Hz, OCH_2CH_3), 2.38 (3H, s, Ar-CH_3), 1.37 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 168.8 (C, O-C=O), 157.7 (C), 149.4 (C), 141.3 (C), 134.8 (C), 133.1 (CH), 131.2 (CH), 129.4 (CH), 126.9 (CH), 124.6 (CH), 124.6 (C), 123.6 (C), 112.6 (CH), 61.0 (CH_2, OCH_2CH_3), 28.3 (CH_2, CH_2Ar), 16.9



90at

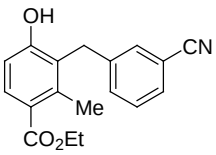
(CH_3, Ar-*C*H_3), 14.3 (CH_3, OCH_2*C*H_3); LRMS m/z 314.00 (M - H^+), calcd $C_{17}H_{17}NO_5$ 315.1107; Anal. calcd for $C_{17}H_{17}NO_5$ (315.11): C, 64.75; H, 5.43; N, 4.44. Found: C, 64.81; H, 5.49; N, 4.40%.

4-Hydroxy-2-methyl-3-(3-nitro-benzyl)-benzoic acid ethyl ester (90ag): Prepared following the procedure **2d** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 150 °C; IR (neat): ν_{max} 3358 (O-*H*), 1678 (O-C=O), 1581, 1526, 1350, 1292, 1178 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.02 (2H, br s), 7.74 (1H, d, *J* = 8.4 Hz), 7.46 (1H, d, *J* = 7.6 Hz), 7.39 (1H, t, *J* = 7.6 Hz), 6.74 (1H, d, *J* = 8.4 Hz); 6.04 (1H, s, O-*H*), 4.33 (2H, q, *J* = 7.2 Hz, OC$H_2$$CH_3$), 4.20 (2H, s, C$H_2$Ar), 2.48 (3H, s, Ar-C$H_3$), 1.37 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 168.2 (C, O-C=O), 156.8 (C), 148.4 (C), 142.2 (C), 141.1 (C), 134.4 (CH), 131.0 (CH), 129.1 (CH), 125.4 (C), 124.0 (C), 123.1 (CH), 121.1 (CH), 112.6 (CH), 60.8 (CH_2, O*C*$H_2$$CH_3$), 31.4 ($CH_2$, *C*$H_2$Ar), 17.0 ($CH_3$, Ar-*C*$H_3$), 14.3 ($CH_3$, OCH_2*C*H_3); LRMS m/z 316.00 (M + H^+), calcd $C_{17}H_{17}NO_5$ 315.1107; HRMS m/z 338.1002 (M + Na), calcd for $C_{17}H_{17}NO_5Na$ 338.1005; Anal. calcd for $C_{17}H_{17}NO_5$ (315.11): C, 64.75; H, 5.43; N, 4.44. Found: C, 64.55; H, 5.38; N, 4.55%.



90ag

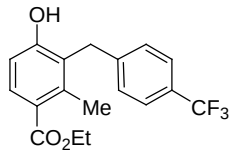
3-(3-Cyano-benzyl)-4-hydroxy-2-methyl-benzoic acid ethyl ester (90af): Prepared following the procedure **2d** and purified by column chromatography using EtOAc/hexane and isolated as a white solid. Mp 116 °C; IR (neat): ν_{max} 3361 (O-*H*), 2229, 1687 (O-C=O), 1678, 1582, 1459, 1291, 1269, 1180, 1156, 1054 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.74 (1H, d, *J* = 8.4 Hz), 7.44 (1H, br s, O-*H*), 7.45 – 7.41 (3H, m), 7.32 (1H, t, *J* = 7.6 Hz), 6.82 (1H, d, *J* = 8.4 Hz); 4.34 (2H, q, *J* = 7.2 Hz, OC$H_2$$CH_3$), 4.14 (2H, s, C$H_2$Ar), 2.46 (3H, s, Ar-C$H_3$), 1.38 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ



90af

168.7 (C, O-C=O), 157.6 (C), 141.8 (C), 140.8 (C), 133.0 (CH), 131.6 (CH), 130.9 (CH), 129.5 (CH), 128.9 (CH), 125.4 (C), 123.1 (C), 119.0 (C), 112.5 (CH), 111.7 (C), 60.8 (CH_2, O*C*H_2CH_3), 31.1 (CH_2, *C*H_2Ar), 17.0 (CH_3, Ar-*C*H_3), 14.2 (CH_3, OCH_2*C*H_3); LRMS m/z 294.00 (M - H^+), calcd $C_{18}H_{17}NO_3$ 295.1208; Anal. calcd for $C_{18}H_{17}NO_3$ (295.12): C, 73.20; H, 5.80; N, 4.74. Found: C, 73.15; H, 5.88; N, 4.81%.

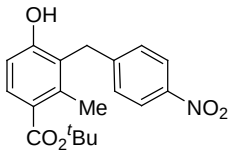
4-Hydroxy-2-methyl-3-(4-trifluoromethyl-benzyl)-benzoic acid ethyl ester (90ad):



90ad

Prepared following the procedure **2d** and purified by column chromatography using EtOAc/hexane and isolated as a white solid. Mp 120 °C; IR (neat): ν_{max} 3347 (O-*H*), 1681 (O-C=O), 1580, 1326, 1262, 1156, 1112, 1068, 646 cm^{-1}; ^{1}H NMR ($CDCl_3$, at 25 °C) δ 7.72 (1H, d, *J* = 8.4 Hz), 7.48 (2H, d, *J* = 8.0 Hz), 7.22 (2H, d, *J* = 8.0 Hz), 6.75 (1H, d, *J* = 8.8 Hz) ; 6.74(1H, s, O-*H*), 4.34 (2H, q, *J* = 7.2 Hz, OC$H_2$$CH_3$), 4.17 (2H, s, C$H_2$Ar), 2.47 (3H, s, Ar-C$H_3$), 1.38 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135, at 40 °C) δ 168.8 (C, O-C=O), 157.3 (C), 144.2 (C), 141.1 (C), 130.7 (CH), 128.4 (2 x CH), 128.3 (CF_3, q, *J* = 32.0 Hz), 126.0 (C), 125.2 (2 x CH, q, *J* = 4.0 Hz), 123.8 (C), 123.0 (C), 112.6 (CH), 60.9 (CH_2, O*C*H_2CH_3), 31.6 (CH_2, *C*H_2Ar), 17.0 (CH_3, Ar-*C*H_3), 14.2 (CH_3, OCH_2*C*H_3); LRMS m/z 339.00 (M + H^+), calcd $C_{18}H_{17}F_3O_3$ 338.1130; HRMS m/z 361.1310 (M + Na), calcd for $C_{18}H_{17}F_3O_3Na$ 361.1028; Anal. calcd for $C_{18}H_{17}F_3O_3$ (338.11): C, 63.90; H, 5.06. Found: C, 63.85; H, 5.11%.

4-Hydroxy-2-methyl-3-(4-nitro-benzyl)-benzoic acid *tert*-butyl ester (90ba):

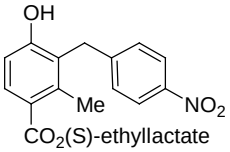


90ba

Prepared following the procedure **2d** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 98 °C; IR (neat): ν_{max} 3387 (O-*H*), 2982, 2930, 1668 (O-C=O), 1593, 1516, 1344, 1285, 1132, 1011, 849 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.04 (2H, d, *J* = 8.8 Hz), 7.59 (1H, d, *J* = 8.4 Hz), 7.24 (2H, d, *J* = 8.4 Hz), 6.84 (1H, br s, O-*H*), 6.71 (1H, d, *J* = 8.4 Hz), 4.17 (2H, s, CH_2Ar), 2.40 (3H, s, Ar-CH_3), 1.58 (9H,

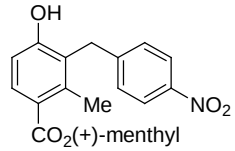
s, 3 x CH_3, O-C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 168.4 (C, O-C=O), 156.7 (C), 148.3 (C), 146.1 (C), 140.0 (C), 130.5 (CH), 128.8 (2 x CH), 125.5 (C), 125.1 (C), 123.5 (2 x CH), 112.4 (CH), 81.5 (C, O-*C*$(CH_3)_3$), 31.7 (CH_2, *C*H_2Ar), 28.2 (3 x CH_3, O-C(*C*H_3)$_3$), 17.1 (CH_3, Ar-*C*H_3); LRMS m/z 342.10 (M - H^+), calcd $C_{19}H_{21}NO_5$ 343.1420; Anal. calcd for $C_{19}H_{21}NO_5$ (343.14): C, 66.46; H, 6.16; N, 4.08. Found: C, 66.35; H, 6.11; N, 4.21%.

4-Hydroxy-2-methyl-3-(4-nitro-benzyl)-benzoic acid 1-ethoxycarbonyl-ethyl ester (90ca): Prepared following the procedure **2d** and purified by column chromatography using EtOAc/hexane and isolated as a colorless liquid; **$[\alpha]^{25}_D$ = +7.6 (*c* 0.3, $CHCl_3$);** IR (neat): ν_{max} 3412 (O-*H*), 2984, 2938, 1717 (O-C=O), 1586, 1520, 1451, 1346, 1098, 754 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.08 (2H, d, *J* = 7.6 Hz), 7.80 (1H, d, *J* = 8.4 Hz), 7.26 (2H, d, *J* = 8.4 Hz), 6.73 (1H, d, *J* = 8.8 Hz), 6.45 (1H, s, O-*H*), 5.26 (1H, br q, *J* = 7.2 Hz, C*H*), 4.24 (2H, br q, *J* = 7.2 Hz, OCH_2CH$_3$), 4.18 (2H, br s, CH_2Ar), 2.45 (3H, s, Ar-CH_3), 1.60 (3H, d, *J* = 7.2 Hz), 1.30 (3H, t, *J* = 7.2 Hz, OCH$_2$CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 171.8 (C, O-C=O), 167.3 (C, O-C=O), 157.8 (C), 148.3 (C), 146.2 (C), 141.6 (C), 131.4 (CH), 128.9 (2 x CH), 125.4 (C), 123.6 (2 x CH), 122.2 (C), 112.7 (CH), 68.9 (CH), 61.7 (CH_2, O*C*H$_2$CH$_3$), 31.7 (CH_2, *C*H_2Ar), 17.1 (CH_3, Ar-*C*H_3), 17.0 (CH_3), 14.1 (CH_3, OCH$_2$*C*H$_3$); LRMS m/z 386.15 (M - H^+), calcd $C_{20}H_{21}NO_7$ 387.1318; Anal. calcd for $C_{20}H_{21}NO_7$ (387.13): C, 62.01; H, 5.46; N, 3.62. Found: C, 62.15; H, 5.51; N, 3.67%.



(+)-**90ca**

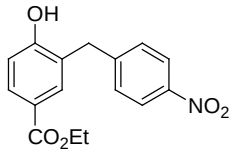
4-Hydroxy-2-methyl-3-(4-nitro-benzyl)-benzoic acid 2-isopropyl-5-methyl-cyclohexyl ester (90da): Prepared following the procedure **2d** and purified by column chromatography using EtOAc/hexane and isolated as a white solid. Mp 150 °C; **$[\alpha]^{25}_D$ = –37.3 (*c* 0.3, $CHCl_3$);** IR (neat): ν_{max} 3403 (O-*H*), 2957, 1672 (O-C=O), 1582, 1516, 1454, 1344, 1294, 1248, 1042, 858 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.09 (2H, d, *J* = 8.0



(–)-**90da**

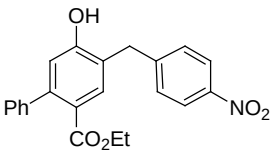
Hz), 7.71 (1H, d, *J* = 8.8 Hz), 7.28 (2H, d, *J* = 8.0 Hz), 6.73 (1H, d, *J* = 8.8 Hz); 5.79 (1H, s, O-*H*), 4.89 (1H, dt, *J* = 10.4, 4.0 Hz), 4.21 (2H, s, CH_2Ar), 2.45 (3H, s, Ar-CH_3), 2.11 (1H, br d, *J* = 11.6 Hz), 2.00-1.93 (1H, m), 1.74 (1H, br s), 1.70 (1H, br s), 1.51 (2H, t, *J* = 10.8 Hz), 1.15-1.04 (2H, m), 0.92 (1H, m), 0.91 (6H, d, *J* = 6.8 Hz, 2 x CH_3), 0.79 (3H, d, *J* = 6.8 Hz, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.7 (C, O-C=O), 156.6 (C), 148.1 (C), 146.3 (C), 141.0 (C), 130.6 (CH), 128.9 (2 x CH), 125.2 (C), 124.6 (C), 123.6 (2 x CH), 112.5 (CH), 74.7 (CH), 47.2 (CH), 41.0 (CH_2), 34.2 (CH_2), 31.7 (CH_2), 31.5 (CH), 26.3 (CH), 23.3 (CH_2), 22.0 (CH_3), 20.9 (CH_3), 17.1 (CH_3), 16.2 (CH_3); LRMS m/z 424.25 (M - H^+), calcd $C_{25}H_{31}NO_5$ 425.2202; HRMS m/z 448.2107 (M + Na), calcd for $C_{25}H_{31}NO_5Na$ 448.2100; Anal. calcd for $C_{25}H_{31}NO_5$ (425.22): C, 70.57; H, 7.34; N, 3.29. Found: C, 70.45; H, 7.28; N, 3.35%.

4-Hydroxy-3-(4-nitro-benzyl)-benzoic acid ethyl ester (90ea): Prepared following the procedure **2d** and purified by column chromatography using EtOAc/hexane and isolated as a yellow solid. Mp 126 °C; IR (neat): ν_{max} 3355 (O-*H*), 1688 (O-C=O), 1607, 1515, 1343, 1297 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.10 (2H, d, *J* = 8.8 Hz), 7.86 (1H, s), 7.84 (1H, dd, *J* = 10.0, 1.6 Hz), 7.37 (2H, d, *J* = 8.4 Hz), 6.82 (1H, d, *J* = 8.0 Hz), 6.23 (1H, br s, O-*H*), 4.35 (2H, q, *J* = 7.2 Hz, OC$H_2$$CH_3$), 4.08 (2H, s, C$H_2$Ar), 1.38 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 166.7 (C, O-C=O), 158.0 (C), 148.0 (C), 146.5 (C), 132.8 (CH), 130.5 (CH), 129.5 (2 x CH), 125.9 (C), 123.7 (2 x CH), 123.1 (C), 115.4 (CH), 61.1 (CH_2, O*C*$H_2$$CH_3$), 36.0 ($CH_2$, *C*$H_2$Ar), 14.4 ($CH_3$, OCH_2*C*H_3); LRMS m/z 300.15 (M - H^+), calcd $C_{16}H_{15}NO_5$ 301.0950; Anal. calcd for $C_{16}H_{15}NO_5$ (301.09): C, 63.78; H, 5.02; N, 4.65. Found: C, 63.85; H, 5.08; N, 4.71%.



90ea

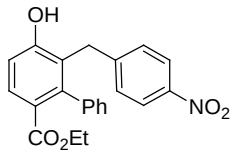
5-Hydroxy-4-(4-nitro-benzyl)-biphenyl-2-carboxylic acid ethyl ester (90fa): Prepared following the procedure **2d** and purified by column chromatography using EtOAc/hexane and isolated as a liquid; IR (neat): ν_{max} 3391 (O-*H*), 2990, 2926, 2853, 1719 (O-C=O),



90fa

1682, 1607, 1520, 1344, 1287, 766, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.13 (2H, d, *J* = 9.2 Hz), 7.72 (1H, s, Ar-*H*), 7.41 (2H, d, *J* = 9.2 Hz), 7.35-7.33 (3H, m), 7.23 (2H, m), 6.71 (1H, s, Ar-*H*), 5.87 (1H, s, O-*H*), 4.10 (2H, s, CH_2Ar), 4.04 (2H, q, *J* = 7.2 Hz, OCH_2CH_3), 0.95 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 168.2 (C, O-C=O), 156.0 (C), 147.9 (C), 146.5 (C), 144.1 (C), 141.1 (C), 133.5 (CH), 129.5 (2 x CH), 128.2 (2 x CH), 127.9 (2 x CH), 127.3 (CH), 124.8 (C), 123.7 (2 x CH), 123.4 (C), 117.8 (CH), 60.8 (CH_2, OCH_2CH_3), 35.7 (CH_2, CH_2Ar), 13.6 (CH_3, OCH_2CH_3); LRMS m/z 378.05 ($M + H^+$), calcd $C_{22}H_{19}NO_5$ 377.1263; Anal. calcd for $C_{22}H_{19}NO_5$ (377.12): C, 70.02; H, 5.07; N, 3.71. Found: C, 70.15; H, 5.11; N, 3.75%.

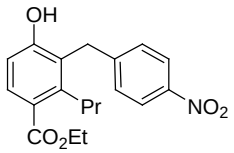
5-Hydroxy-6-(4-nitro-benzyl)-biphenyl-2-carboxylic acid ethyl ester (90ga):



90ga

Prepared following the procedure **2d** and purified by column chromatography using EtOAc/hexane and isolated as a white solid. Mp 144 °C; IR (neat): ν_{max} 3407 (O-*H*), 2976, 1694 (O-C=O), 1588, 1516, 1020, 941, 858, 766 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.98 (2H, d, *J* = 8.0 Hz), 7.77 (1H, d, *J* = 8.4 Hz), 7.31-7.27 (3H, m), 7.03-6.98 (4H, m), 6.86 (1H, d, *J* = 8.4 Hz), 6.69 (1H, s, O-*H*), 3.95 (2H, q, *J* = 7.2 Hz, OCH_2CH_3), 3.92 (2H, s, CH_2Ar), 0.89 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 168.5 (C, O-C=O), 157.2 (C), 148.9 (C), 146.0 (C), 145.0 (C), 139.6 (C), 130.5 (CH), 129.0 (2 x CH), 128.6 (2 x CH), 127.8 (2 x CH), 127.2 (CH), 125.0 (C), 124.1 (C), 123.2 (2 x CH), 114.3 (CH), 60.8 (CH_2, OCH_2CH_3), 32.6 (CH_2, CH_2Ar), 13.5 (CH_3, OCH_2CH_3); LRMS m/z 376.45 ($M - H^+$), calcd $C_{22}H_{19}NO_5$ 377.1263; Anal. calcd for $C_{22}H_{19}NO_5$ (377.12): C, 70.02; H, 5.07; N, 3.71. Found: C, 70.15; H, 5.12; N, 3.76%.

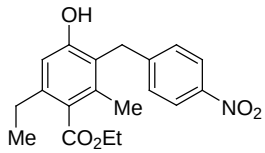
4-Hydroxy-3-(4-nitro-benzyl)-2-propyl-benzoic acid ethyl ester (90ha): Prepared following the procedure **2d** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 134 °C; IR (neat): ν_{max} 3360 (O-*H*), 2963, 2928, 1684 (O-C=O), 1578, 1516, 1470, 1346, 1262, 1009, 733 cm^{-1}; ^1H NMR ($CDCl_3$) δ



90ha

8.07 (2H, d, *J* = 8.4 Hz), 7.74 (1H, d, *J* = 8.4 Hz), 7.26 (2H, d, *J* = 8.0 Hz), 6.76 (1H, s, O-*H*), 6.75 (1H, d, *J* = 8.4 Hz), 4.33 (2H, q, *J* = 7.2 Hz, OC$H_2$$CH_3$), 4.20 (2H, s, C$H_2$Ar), 2.86 (2H, t, *J* = 7.6 Hz, ArC$H_2$$CH_2$$CH_3$), 1.52-1.42 (2H, m, Ar$CH_2CH_2$$CH_3$), 1.37 (3H, t, *J* = 7.2 Hz, OCH_2CH_3), 0.94 (3H, t, *J* = 7.6 Hz, Ar$CH_2$$CH_2CH_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 168.5 (C, O-C=O), 157.5 (C), 148.8 (C), 146.1 (C), 145.5 (C), 131.4 (CH), 128.8 (2 x CH), 124.6 (C), 123.5 (2 x CH), 123.1 (C), 112.7 (CH), 60.9 (CH_2, O*C*$H_2$$CH_3$), 32.3 ($CH_2$, *C*$H_2$Ar), 31.3 ($CH_2$, Ar*C*$H_2$$CH_2$$CH_3$), 24.5 ($CH_2$, Ar$CH_2$*C*$H_2$$CH_3$), 14.5 ($CH_3$, OCH_2*C*H_3), 14.2 (CH_3, Ar$CH_2$$CH_2$*C*$H_3$); LRMS m/z 342.10 (M - H^+), calcd $C_{19}H_{21}NO_5$ 343.1420; HRMS m/z 366.1317 (M + Na), calcd for $C_{19}H_{21}NO_5Na$ 366.1318; Anal. calcd for $C_{19}H_{21}NO_5$ (343.14): C, 66.46; H, 6.16; N, 4.08. Found: C, 66.52; H, 6.21; N, 4.15%.

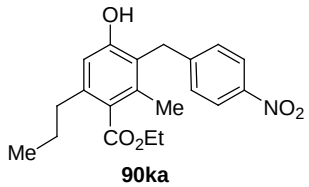
6-Ethyl-4-hydroxy-2-methyl-3-(4-nitro-benzyl)-benzoic acid ethyl ester (90ja):



90ja

Prepared following the procedure **2d** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 102 °C; IR (neat): ν_{max} 3401 (O-*H*), 2974, 2940, 1715 (O-C=O), 1696, 1601, 1520, 1344, 1152, 1051, 858 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.06 (2H, d, *J* = 8.8 Hz), 7.26 (2H, d, *J* = 8.4 Hz), 6.60 (1H, s, Ar-*H*), 5.80 (1H, brs, O-*H*), 4.37 (2H, q, *J* = 7.2 Hz, OC$H_2$$CH_3$), 4.10 (2H, s, C$H_2$Ar), 2.54 (2H, q, *J* = 7.6 Hz, ArC$H_2$$CH_3$), 2.15 (3H, s, Ar-C$H_3$), 1.37 (3H, t, *J* = 7.2 Hz, OCH_2CH_3), 1.18 (3H, t, *J* = 7.6 Hz, ArCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 170.8 (C, O-C=O), 154.7 (C), 148.2 (C), 146.2 (C), 141.1 (C), 135.4 (C), 128.9 (2 x CH), 127.5 (C), 123.5 (2 x CH), 122.0 (C), 113.0 (CH), 61.2 (CH_2, O*C*$H_2$$CH_3$), 31.6 ($CH_2$, *C*$H_2$Ar), 26.6 ($CH_2$, *C*$H_2$$CH_3$), 16.8 ($CH_3$, Ar-*C*$H_3$), 15.3 ($CH_3$, CH_2*C*H_3), 14.2 (CH_3, OCH_2*C*H_3); LRMS m/z 342.10 (M - H^+), calcd $C_{19}H_{21}NO_5$ 343.1420; HRMS m/z 366.1318 (M + Na), calcd for $C_{19}H_{21}NO_5Na$ 366.1318; Anal. calcd for $C_{19}H_{21}NO_5$ (343.14): C, 66.46; H, 6.16; N, 4.08. Found: C, 66.55; H, 6.13; N, 4.12%.

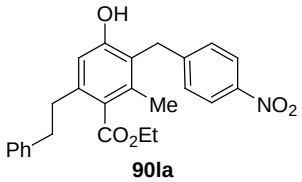
4-Hydroxy-2-methyl-3-(4-nitro-benzyl)-6-propyl-benzoic acid ethyl ester (90ka):



90ka

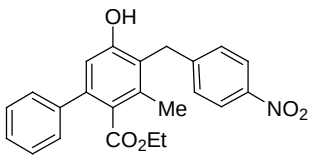
Prepared following the procedure **2d** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 80 °C; IR (neat): ν_{max} 3385 (O-*H*), 3056, 2963, 2870, 1717 (O-C=O), 1694, 1599, 1518, 1344, 1152, 1051, 858 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.04 (2H, d, *J* = 8.4 Hz), 7.25 (2H, d, *J* = 8.8 Hz), 6.53 (1H, s, Ar-*H*); 5.86 (1H, br s, O-*H*), 4.37 (2H, q, *J* = 7.2 Hz, OCH_2CH_3), 4.10 (2H, s, CH_2Ar), 2.48 (2H, t, *J* = 7.6 Hz, $ArCH_2CH_2CH_3$), 2.15 (3H, s, Ar-CH_3), 1.63-1.53 (2H, m, $ArCH_2CH_2CH_3$), 1.37 (3H, t, *J* = 7.2 Hz, OCH_2CH_3), 0.93 (3H, t, *J* = 7.2 Hz, $ArCH_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 170.9 (C, O-C=O), 154.5 (C), 148.2 (C), 146.2 (C), 139.6 (C), 135.4 (C), 128.9 (2 x CH), 127.6 (C), 123.5 (2 x CH), 122.0 (C), 113.7 (CH), 61.2 (CH_2, OCH_2CH_3), 35.6 (CH_2, $ArCH_2CH_2CH_3$), 31.6 (CH_2, CH_2Ar), 24.3 (CH_2, $ArCH_2CH_2CH_3$), 16.8 (CH_3, Ar-CH_3), 14.2 (CH_3, OCH_2CH_3), 14.0 (CH_3, $ArCH_2CH_2CH_3$); LRMS m/z 356.30 ($M - H^+$), calcd $C_{20}H_{23}NO_5$ 357.1576; Anal. calcd for $C_{20}H_{23}NO_5$ (357.15): C, 67.21; H, 6.49; N, 3.92. Found: C, 67.35; H, 6.41; N, 4.07%.

4-Hydroxy-2-methyl-3-(4-nitro-benzyl)-6-phenethyl-benzoic acid ethyl ester (90la):



90la

Prepared following the procedure **2d** and purified by column chromatography using EtOAc/hexane and isolated as a yellow liquid; IR (neat): ν_{max} 3410 (O-*H*), 2928, 1719 (O-C=O), 1694, 1599, 1518, 1454, 1344, 1150, 858 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.06 (2H, d, *J* = 8.4 Hz), 7.30-7.10 (7H, m), 6.49 (1H, s, Ar-*H*), 5.72 (1H, br s, O-*H*), 4.38 (2H, q, *J* = 7.2 Hz, OCH_2CH_3), 4.11 (2H, s, CH_2Ar), 2.89-2.78 (4H, m), 2.17 (3H, s, Ar-CH_3), 1.36 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 170.5 (C, O-C=O), 154.5 (C), 148.1 (C), 146.2 (C), 141.4 (C), 138.8 (C), 135.7 (C), 128.9 (2 x CH), 128.4 (2 x CH), 128.3 (2 x CH), 127.7 (C), 126.1 (CH), 123.6 (2 x CH), 122.4 (C), 113.8 (CH), 61.3 (CH_2, OCH_2CH_3), 37.5 (CH_2), 35.7 (CH_2), 31.6 (CH_2, CH_2Ar), 16.9 (CH_3, Ar-CH_3), 14.2 (CH_3, OCH_2CH_3); LRMS m/z 418.25 (M -

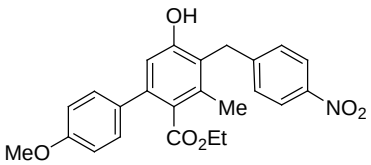


90ma

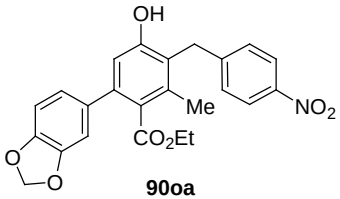
H^+), calcd $C_{25}H_{25}NO_5$ 419.1733; HRMS m/z 442.1632 (M + Na), calcd for $C_{25}H_{25}NO_5Na$ 442.1631; Anal. calcd for $C_{25}H_{25}NO_5$ (419.17): C, 71.58; H, 6.01; N, 3.34. Found: C, 71.48; H, 6.11; N, 3.31%.

5-Hydroxy-3-methyl-4-(4-nitro-benzyl)-biphenyl-2-carboxylic acid ethyl ester (90ma): Prepared following the procedure **2d** and purified by column chromatography using EtOAc/hexane and isolated as a liquid; IR (neat): ν_{max} 3403 (O-*H*), 2978, 2930, 1688 (O-C=O), 1597, 1518, 1344, 1263, 1171, 1053 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.02 (2H, d, *J* = 8.4 Hz), 7.28-7.24 (7H, m); 6.69 (1H, br s, O-*H*), 6.59 (1H, s, Ar-*H*), 4.12 (2H, s, C*H*$_2$Ar), 4.00 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 2.21 (3H, s, Ar-C*H*$_3$), 0.90 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 170.9 (C, O-C=O), 154.8 (C), 148.0 (C), 146.1 (C), 140.4 (C), 140.3 (C), 136.2 (C), 128.9 (2 x CH), 128.1 (2 x CH), 128.0 (2 x CH), 127.4 (CH), 126.6 (C), 123.6 (C), 123.5 (2 x CH), 114.2 (CH), 61.3 (CH$_2$, O*C*H$_2$CH$_3$), 31.6 (CH$_2$, *C*H$_2$Ar), 16.7 (CH$_3$, Ar-*C*H$_3$), 13.4 (CH$_3$, OCH$_2$*C*H$_3$); LRMS m/z 390.15 (M - H^+), calcd $C_{23}H_{21}NO_5$ 391.1420; Anal. calcd for $C_{23}H_{21}NO_5$ (391.14): C, 70.58; H, 5.41; N, 3.58. Found: C, 70.45; H, 5.45; N, 3.65%.

5-Hydroxy-4'-methoxy-3-methyl-4-(4-nitro-benzyl)-biphenyl-2-carboxylic acid ethyl ester (90na): Prepared following the procedure **2d** and purified by column chromatography using EtOAc/hexane and isolated as a yellow liquid; IR (neat): ν_{max} 3407 (O-*H*), 2984, 2934, 1721 (O-C=O), 1692, 1599, 1516, 1344, 1250, 1028 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.08 (2H, d, *J* = 8.4 Hz), 7.30 (2H, d, *J* = 8.4 Hz), 7.23 (2H, d, *J* = 8.4 Hz), 6.87 (2H, d, *J* = 8.4 Hz), 6.62 (1H, s, Ar-*H*), 6.17 (1H, br s, O-*H*), 4.16 (2H, s, C*H*$_2$Ar), 4.05 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 3.82 (3H, s, O-C*H*$_3$), 2.22 (3H, s, Ar-C*H*$_3$), 0.99 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 170.6 (C, O-C=O), 159.1 (C), 154.5 (C), 148.0 (C), 146.2 (C), 139.9 (C), 136.1 (C), 132.9 (C), 129.2 (2 x CH), 129.0 (2 x CH), 127.2 (C), 123.6 (2 x CH), 123.2 (C), 114.2 (CH), 113.6 (2 x CH), 61.1 (CH$_2$, O*C*H$_2$CH$_3$), 55.3 (CH$_3$,



90na

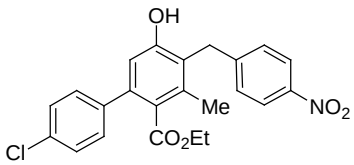


90oa

O*C*H$_3$), 31.7 (CH$_2$, *C*H$_2$Ar), 16.8 (CH$_3$, Ar-*C*H$_3$), 13.7 (CH$_3$, OCH$_2$*C*H$_3$); LRMS m/z 420.25 (M - H$^+$), calcd $C_{24}H_{23}NO_6$ 421.1525; Anal. calcd for $C_{24}H_{23}NO_6$ (421.15): C, 68.40; H, 5.50; N, 3.32. Found: C, 68.45; H, 5.46; N, 3.37%.

6-Benzo[1,3]dioxol-5-yl-4-hydroxy-2-methyl-3-(4-nitro-benzyl)-benzoic acid ethyl ester (90oa): Prepared following the procedure **2d** and purified by column chromatography using EtOAc/hexane and isolated as a yellow liquid; IR (neat): ν_{max} 3393 (O-*H*), 2982, 1717 (O-C=O), 1599, 1520, 1480, 1344, 1240, 1040, 858 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.05 (2H, d, *J* = 8.4 Hz), 7.28 (2H, d, *J* = 8.4 Hz), 6.76 (2H, d, *J* = 6.4 Hz), 6.75 (1H, s, Ar-*H*), 6.60 (1H, s, Ar-*H*), 6.60 (1H, br s, O-*H*), 6.00 (2H, s, OC*H*$_2$O), 4.14 (2H, s, C*H*$_2$Ar), 4.10 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 2.21 (3H, s, Ar-*CH*$_3$), 1.05 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 170.7 (C, O-C=O), 154.8 (C), 148.1 (C), 147.5 (C), 147.1 (C), 146.3 (C), 139.8 (C), 136.1 (C), 134.4 (C), 129.0 (2 x CH), 127.0 (C), 123.6 (2 x CH, C), 121.7 (CH), 114.2 (CH), 108.8 (CH), 108.1 (CH), 101.1 (CH$_2$, O*C*H$_2$O), 61.3 (CH$_2$, O*C*H$_2$CH$_3$), 31.7 (CH$_2$, *C*H$_2$Ar), 16.8 (CH$_3$, Ar-*C*H$_3$), 13.8 (CH$_3$, OCH$_2$*C*H$_3$); LRMS m/z 434.30 (M - H$^+$), calcd $C_{24}H_{21}NO_7$ 435.1318; HRMS m/z 458.1218 (M + Na), calcd for $C_{24}H_{21}NO_7Na$ 458.1216; Anal. calcd for $C_{24}H_{21}NO_7$ (435.13): C, 66.20; H, 4.86; N, 3.22. Found: C, 66.15; H, 4.80; N, 3.28%.

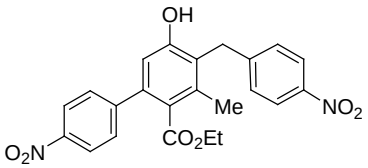
4'-Chloro-5-hydroxy-3-methyl-4-(4-nitro-benzyl)-biphenyl-2-carboxylic acid ethyl ester (90pa): Prepared following the procedure **2d** and purified by column chromatography using EtOAc/hexane and isolated as a yellow liquid; IR (neat): ν_{max} 3391 (O-*H*), 2978, 2934, 1713 (O-C=O), 1690, 1599, 1520, 1344, 1167, 829 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.06 (2H, d, *J* = 8.0 Hz), 7.30-7.28 (4H, m), 7.20 (2H, d, *J* = 7.6 Hz); 6.69 (1H, br s, O-*H*), 6.61 (1H, s, Ar-*H*), 4.15 (2H, s, C*H*$_2$Ar), 4.04 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 2.23 (3H, s, Ar-C*H*$_3$), 0.99 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 170.6 (C, O-C=O), 154.9 (C), 147.9 (C),



90pa

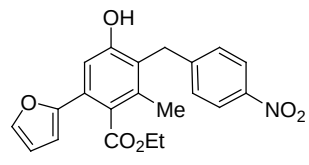
146.2 (C), 138.9 (2 x C), 136.4 (C), 133.5 (C), 129.4 (2 x CH), 128.9 (2 x CH), 128.3 (2 x CH), 126.6 (C), 124.1 (C), 123.5 (2 x CH), 114.0 (CH), 61.4 (CH_2, O*C*H_2CH_3), 31.6 (CH_2, *C*H_2Ar), 16.8 (CH_3, Ar-*C*H_3), 13.6 (CH_3, OCH_2*C*H_3); LRMS m/z 426.00 (M + H^+), calcd $C_{23}H_{20}ClNO_5$ 425.1030; Anal. calcd for $C_{23}H_{20}ClNO_5$ (425.10): C, 64.87; H, 4.73; N, 3.29. Found: C, 64.75; H, 4.76; N, 3.32%.

5-Hydroxy-3-methyl-4'-nitro-4-(4-nitro-benzyl)-biphenyl-2-carboxylic acid ethyl ester (90qa): Prepared following the procedure **2d** and purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 168 °C; IR (neat): ν_{max} 3437 (O-*H*), 2976, 1715 (O-C=O), 1686, 1597, 1518, 1344, 910, 853, 735 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.19 (2H, d, *J* = 8.0 Hz), 8.07 (2H, d, *J* = 8.0 Hz), 7.45 (2H, d, *J* = 8.0 Hz), 7.31 (2H, d, *J* = 8.0 Hz), 6.71 (1H, br s, O-*H*), 6.68 (1H, s, Ar-*H*), 4.19 (2H, s, C*H*$_2$Ar), 4.05 (2H, q, *J* = 6.8 Hz, OC*H*$_2$$CH_3$), 2.26 (3H, s, Ar-C*H*$_3$), 0.99 (3H, t, *J* = 6.8 Hz, OCH_2C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 170.0 (C, O-C=O), 155.0 (C), 147.6 (C), 147.3 (C), 147.0 (C), 146.2 (C), 137.9 (C), 137.0 (C), 129.0 (2 x CH), 128.9 (2 x CH), 126.5 (C), 125.1 (C), 123.6 (2 x CH), 123.4 (2 x CH), 113.9 (CH), 61.5 (CH_2, O*C*H_2CH_3), 31.7 (CH_2, *C*H_2Ar), 16.8 (CH_3, Ar-*C*H_3), 13.6 (CH_3, OCH_2*C*H_3); LRMS m/z 435.10 (M – H^+), calcd $C_{23}H_{20}N_2O_7$ 436.1271; Anal. calcd for $C_{23}H_{20}N_2O_7$ (436.12): C, 63.30; H, 4.62; N, 6.42. Found: C, 63.38; H, 4.55; N, 6.45%.



90qa

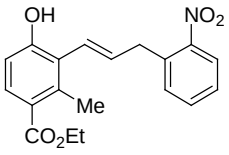
6-Furan-2-yl-4-hydroxy-2-methyl-3-(4-nitro-benzyl)-benzoic acid ethyl ester (90ra): Prepared following the procedure **2d** and purified by column chromatography using EtOAc/hexane and isolated as a yellow liquid; IR (neat): ν_{max} 3382 (O-*H*), 2984, 2938, 2255, 1694 (O-C=O), 1599, 1516, 1344, 1154, 1111, 1016, 860 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.99 (2H, d, *J* = 8.4 Hz), 7.36 (1H, s), 7.19 (2H, d, *J* = 8.0 Hz), 6.99 (1H, br s, O-*H*), 6.91 (1H, s), 6.39 (2H, m), 4.34 (2H, q, *J* = 7.2 Hz,



90ra

OC*H*$_2$CH$_3$), 4.07 (2H, s, C*H*$_2$Ar), 2.16 (3H, s, Ar-C*H*$_3$), 1.27 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 171.4 (C, O-C=O), 154.9 (C), 151.6 (C), 147.9 (C), 146.1 (C), 142.3 (CH), 135.9 (C), 128.8 (2 x CH), 127.8 (C), 124.3 (C), 124.1 (C), 123.4 (2 x CH), 111.5 (CH), 110.9 (CH), 107.4 (CH), 61.8 (CH$_2$, O*C*H$_2$CH$_3$), 31.6 (CH$_2$, *C*H$_2$Ar), 16.4 (CH$_3$, Ar-*C*H$_3$), 13.9 (CH$_3$, OCH$_2$*C*H$_3$); LRMS m/z 382.00 (M + H$^+$), calcd $C_{21}H_{19}NO_6$ 381.1212; HRMS m/z 404.1110 (M + Na), calcd for $C_{21}H_{19}NO_6Na$ 404.1110; Anal. calcd for $C_{21}H_{19}NO_6$ (381.12): C, 66.13; H, 5.02; N, 3.67. Found: C, 66.25; H, 5.09; N, 3.71%.

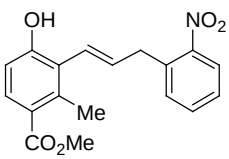
4-Hydroxy-2-methyl-3-[3-(2-nitro-phenyl)-propenyl]-benzoic acid ethyl ester



90aq

(90aq): Prepared following the procedure **2d** and purified by column chromatography using EtOAc/hexane and isolated as a white solid. Mp 112 °C; IR (neat): ν_{max} 3359 (O-*H*), 2981, 2925, 1677 (O-C=O), 1579, 1519, 1353, 1284, 1246, 1160, 1051 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.98 (1H, d, *J* = 8.0 Hz), 7.73 (1H, d, *J* = 8.4 Hz), 7.60 (1H, t, *J* = 7.6 Hz), 7.44 (1H, d, *J* = 8.0 Hz), 7.43 (1H, t, *J* = 7.6 Hz), 6.78 (1H, d, *J* = 8.8 Hz), 6.28 (1H, d, *J* = 16.4 Hz), 6.08 (1H, dt, *J* = 16.4, 6.0 Hz), 5.92 (1H, br s, O-*H*), 4.30 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 3.90 (2H, d, *J* = 6.0 Hz), 2.45 (3H, s, Ar-C*H*$_3$), 1.36 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 167.7 (C, O-C=O), 155.7 (C), 149.2 (C), 140.0 (C), 135.2 (CH), 134.0 (C), 133.5 (CH), 132.2 (CH), 131.3 (CH), 127.9 (CH), 126.0 (CH), 125.0 (CH), 124.7 (C), 122.7 (C), 112.5 (CH), 60.5 (CH$_2$, O*C*H$_2$CH$_3$), 36.7 (CH$_2$, *C*H$_2$Ar), 18.1 (CH$_3$, Ar-*C*H$_3$), 14.3 (CH$_3$, OCH$_2$*C*H$_3$); LRMS m/z 342.00 (M + H$^+$), calcd $C_{19}H_{19}NO_5$ 341.1263; HRMS m/z 364.1164 (M + Na), calcd for $C_{19}H_{19}NO_5Na$ 364.1161; Anal. calcd for $C_{19}H_{19}NO_5$ (341.12): C, 66.85; H, 5.61; N, 4.10. Found: C, 66.91; H, 5.57; N, 4.18%.

4-Hydroxy-2-methyl-3-[3-(2-nitro-phenyl)-propenyl]-benzoic acid methyl ester

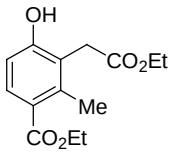


90sq

(90sq): Prepared following the procedure **2d** and purified by column chromatography using EtOAc/hexane and isolated as a

yellow solid. Mp 136 °C; IR (neat): ν_{max} 3352 (O-*H*), 2955, 1736, 1672 (O-C=O), 1580, 1524, 1435, 1346, 1252, 1196, 1034, 984 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.99 (1H, dd, *J* = 9.2, 1.6 Hz), 7.74 (1H, d, *J* = 8.8 Hz), 7.61 (1H, dt, *J* = 8.4, 1.2 Hz), 7.45 (1H, d, *J* = 7.2 Hz), 7.43 (1H, dt, *J* = 8.4, 1.2 Hz), 6.78 (1H, d, *J* = 8.8 Hz); 6.27 (1H, d, *J* = 16.4 Hz), 6.09 (1H, td, *J* = 16.4, 6.0 Hz), 5.83 (1H, s, O-*H*), 3.91 (2H, dd, *J* = 6.0, 1.2 Hz), 3.84 (3H, s, OC*H*$_3$), 2.45 (3H, s, Ar-C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 168.0 (C, O-C=O), 155.7 (C), 149.3 (C), 140.2 (C), 135.4 (CH), 133.9 (C), 133.5 (CH), 132.2 (CH), 131.4 (CH), 128.0 (CH), 126.0 (CH), 125.1 (CH), 124.7 (C), 122.3 (C), 112.5 (CH), 51.7 (CH_3, O*C*H$_3$), 36.8 (CH_2, *C*H$_2$Ar), 18.1 (CH_3, Ar-*C*H$_3$); LRMS m/z 328.20 (M + H^+), calcd $C_{18}H_{17}NO_5$ 327.1107; Anal. calcd for $C_{18}H_{17}NO_5$ (327.11): C, 66.05; H, 5.23; N, 4.28. Found: C, 66.12; H, 5.28; N, 4.21%.

3-Ethoxycarbonylmethyl-4-hydroxy-benzoic acid ethyl ester (90au): Prepared following the procedure **2d** and purified by column chromatography using EtOAc/hexane and isolated as a liquid; IR (neat): ν_{max} 3370 (O-*H*), 2982, 1713 (O-C=O), 1588, 1447, 1370, 1258, 1181, 1055, 783 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.71 (1H, d, *J* = 8.4 Hz), 7.37 (1H, br s, O-*H*), 6.76 (1H, d, *J* = 8.8 Hz), 4.32 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 4.19 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 3.77 (2H, s, C*H*$_2$Ar), 2.56 (3H, s, Ar-C*H*$_3$), 1.37 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$), 1.28 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 173.2 (C, O-C=O), 168.0 (C, O-C=O), 157.9 (C), 140.4 (C), 131.3 (CH), 123.9 (C), 121.2 (C), 114.1 (CH), 61.8 (CH_2, O*C*H$_2$CH$_3$), 60.6 (CH_2, O*C*H$_2$CH$_3$), 32.9 (CH_2, *C*H$_2$Ar), 17.1 (CH_3, Ar-*C*H$_3$), 14.3 (CH_3, OCH$_2$*C*H$_3$), 14.1 (CH_3, OCH$_2$*C*H$_3$); LRMS m/z 265.20 (M - H^+), calcd $C_{14}H_{18}O_5$ 266.1154; Anal. calcd for $C_{14}H_{18}O_5$ (266.11): C, 63.15; H, 6.81. Found: C, 63.22; H, 6.85%.

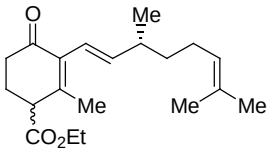


90au

2e: (*S*)-1-(2-Pyrrolidinylmethyl)pyrrolidine-catalyzed cascade Claisen-Schmidt and isomerization reactions: In an ordinary glass vial equipped with a magnetic stirring bar, to 1.0 mmol of the Hagemann's ester **88a** was added 1.0 mL of DMSO

solvent, and then the catalyst (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine **2i** (0.1 mmol, 16.3 µL) was added and then 0.5 mmol of aldehyde **28v-28b'** was added in one-portion and the reaction mixture was stirred at 25 °C for the time indicated in Table 8. The crude reaction mixture was worked up with aqueous NH_4Cl solution and the aqueous layer was extracted with dichloromethane (2 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The pure cascade products **92** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

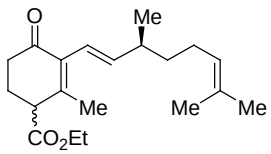
(3*R*)-3-(3,7-Dimethyl-octa-1,6-dienyl)-2-methyl-4-oxo-cyclohex-2-enecarboxylic acid ethyl ester (92av): Prepared following the procedure **2e** and purified by column chromatography using EtOAc/hexane and isolated as a colorless oily liquid. **$[\alpha]^{25}_D$ = –43.6 (*c* 0.54, $CHCl_3$);** IR (neat): ν_{max} 2960, 2912, 1730 (C=O), 1673 (O-C=O), 1157 cm^{-1}; **^{1}H NMR ($CDCl_3$, 1:1 mixture of diastereomers, at room temperature)** δ 6.02 (2H, d, *J* = 16.0 Hz), 5.76 (2H, dd, *J* = 16.0, 8.0 Hz), 5.08 (2H, t, *J* = 7.2 Hz), 4.19 (4H, q, *J* = 7.2 Hz, 2 x OC*H*$_2$CH$_3$), 3.33 (2H, t, *J* = 4.8 Hz), 2.64-2.55 (2H, m), 2.38 (2H, td, *J* = 16.8, 5.6 Hz), 2.27-2.18 (4H, m), 2.05 (6H, s, 2 x olefinic-C*H*$_3$), 1.98 (4H, m), 1.66 (6H, s, 2 x C*H*$_3$), 1.58 (6H, s, 2 x C*H*$_3$), 1.35 (4H, m), 1.27 (6H, t, *J* = 7.2 Hz, 2 x OCH$_2$C*H*$_3$), 1.02 (6H, d, *J* = 6.8 Hz, 2 x CHC*H*$_3$); **^{13}C NMR ($CDCl_3$, 1:1 mixture of diastereomers, at room temperature)** δ 197.3 (2 x C, C=O), 172.2 (2 x C, O-C=O), 149.6 (2 x C), 143.6 (CH), 143.5 (CH), 134.9 (2 x C), 131.2 (2 x C), 124.5 (2 x CH), 120.5 (2 x CH), 61.2 (2 x CH$_2$, O*C*H$_2$CH$_3$), 48.1 (CH), 48.0 (CH), 37.5 (2 x CH), 36.9 (2 x CH$_2$), 35.22 (CH$_2$), 35.16 (CH$_2$), 25.8 (2 x CH$_2$), 25.7 (2 x CH$_3$, olefinic-*C*H$_3$), 25.2 (2 x CH$_2$), 21.5 (2 x CH$_3$, olefinic-*C*H$_3$), 20.4 (2 x CH$_3$, olefinic-*C*H$_3$), 17.6 (2 x CH$_3$), 14.1 (2 x CH$_3$, OCH$_2$*C*H$_3$); **^{1}H NMR ($CDCl_3$, 1:1 mixture of diastereomers, at –40 °C)** δ 6.07 (1H, d, *J* = 16.4 Hz), 6.06 (1H, d, *J* = 16.4 Hz), 5.70 (1H, dd, *J* = 8.0, 4.0 Hz), 5.66 (1H, dd, *J* = 8.4, 4.0 Hz), 5.11 (2H, t, *J* = 6.4 Hz), 4.22 (4H, q, *J* = 7.2 Hz, 2 x OC*H*$_2$CH$_3$), 3.41 (2H, br s), 2.66-2.58 (2H, m), 2.45 (2H, td, *J* = 17.2, 4.8 Hz), 2.27-2.24 (4H, m), 2.10 (6H, s, 2 x olefinic-C*H*$_3$), 2.03-1.95



(-)-92av
E/*Z* = >99:1
dr = 1:1

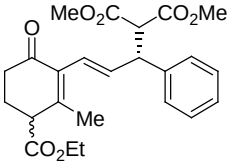
(4H, m), 1.70 (6H, s, 2 x C*H*$_3$), 1.61 (6H, s, 2 x C*H*$_3$), 1.38-1.30 (10H, m), 1.05 (6H, d, *J* = 6.4 Hz, 2 x CHC*H*$_3$); **^{13}C NMR (CDCl$_3$, 1:1 mixture of diastereomers, at –40 °C)** δ 198.16 (C, C=O), 198.13 (C, C=O), 172.4 (C, O-C=O), 172.3 (C, O-C=O), 150.5 (2 x C), 143.7 (CH), 143.6 (CH), 134.8 (2 x C), 131.6 (2 x C), 124.2 (2 x CH), 120.4 (CH), 120.3 (CH), 61.4 (2 x CH$_2$, OC*H*$_2$CH$_3$), 47.8 (CH), 47.6 (CH), 37.6 (CH), 37.5 (CH), 36.7 (2 x CH$_2$), 35.1 (CH$_2$), 34.9 (CH$_2$), 25.84 (2 x CH$_2$), 25.80 (2 x CH$_3$, olefinic-*C*H$_3$), 25.0 (CH$_2$), 24.9 (CH$_2$), 22.01 (CH$_3$, olefinic-*C*H$_3$), 21.98 (CH$_3$, olefinic-*C*H$_3$), 20.60 (CH$_3$, olefinic-*C*H$_3$), 20.55 (CH$_3$, olefinic-*C*H$_3$), 17.7 (2 x CH$_3$), 14.1 (2 x CH$_3$, OCH$_2$*C*H$_3$); LRMS m/z 319.30 (M + H$^+$), calcd C$_{20}$H$_{30}$O$_3$ 318.2195; HRMS m/z 357.1843 (M + K), calcd for C$_{20}$H$_{30}$O$_3$K 357.1832; Anal. calcd for C$_{20}$H$_{30}$O$_3$ (318.21): C, 75.43; H, 9.50. Found: C, 75.52; H, 9.48%.

(3*S*)-3-(3,7-Dimethyl-octa-1,6-dienyl)-2-methyl-4-oxo-cyclohex-2-enecarboxylic acid ethyl ester (92aw): Prepared following the procedure **2e** and purified by column chromatography using EtOAc/hexane and isolated as a colorless oily liquid. **[α]$^{25}_D$ = +45.6 (*c* 0.43, CHCl$_3$);** IR (neat): ν$_{max}$ 2960, 2912, 1730 (C=O), 1673 (O-C=O), 1157 cm^{-1}.



(+)-92aw
E/*Z* = >99:1
dr = 1:1

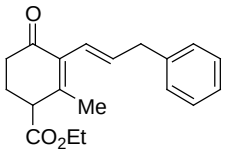
2-[3-(3-Ethoxycarbonyl-2-methyl-6-oxo-cyclohex-1-enyl)-1-phenyl-allyl]-malonic acid dimethyl ester (92ax): Prepared following the procedure **2e** and purified by column chromatography using EtOAc/hexane and isolated as a yellow liquid. **[α]$^{25}_D$ = +19.8 (*c* 0.90, CHCl$_3$);** IR (neat): ν$_{max}$ 2953, 1752, 1721 (C=O), 1674 (O-C=O), 1601, 1437, 1161, 1024, 768, 702 cm^{-1}; **^{1}H NMR (CDCl$_3$, 1:1 mixture of diastereomers)** δ 7.31-7.25 (8H, m, Ph-*H*), 7.20 (2H, t, *J* = 6.8 Hz), 6.18 (4H, m), 4.25-4.10 (2H, m), 4.19 (4H, q, *J* = 7.2 Hz, 2 x OC*H*$_2$CH$_3$), 3.92 (2H, d, *J* = 10.8 Hz), 3.75 (6H, s, 2 x OC*H*$_3$), 3.51 (6H, s, 2 x OC*H*$_3$), 3.31 (2H, t, *J* = 5.2 Hz), 2.62-2.53 (2H, m), 2.35 (2H, td, *J* = 16.8, 4.8 Hz), 2.27-2.13 (4H, m), 1.98 (6H, s, 2 x olefinic-C*H*$_3$), 1.27



(+)-92ax
E/*Z* = >99:1
dr = 1:1

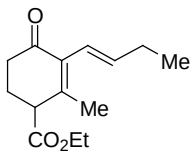
(6H, t, *J* = 6.8 Hz, 2 x OCH_2CH_3); **^{13}C NMR ($CDCl_3$, 1:1 mixture of diastereomers)** δ 196.58 (C, C=O), 196.55 (C, C=O), 171.9 (2 x C, 2 x O-C=O), 168.18 (C, O-C=O), 168.16 (C, O-C=O), 167.8 (2 x C, 2 x O-C=O), 151.0 (2 x C), 140.04 (C), 140.01 (C), 135.8 (CH), 135.7 (CH), 133.9 (2 x C), 128.6 (4 x CH), 127.9 (2 x CH), 127.8 (2 x CH), 127.1 (2 x CH), 124.4 (2 x CH), 61.3 (2 x CH_2, 2 x OCH_2CH_3), 57.6 (2 x CH), 52.6 (2 x CH_3, OCH_3), 52.4 (2 x CH_3, OCH_3), 49.92 (CH), 49.87 (CH), 48.1 (2 x CH), 35.2 (CH_2), 35.1 (CH_2), 25.12 (CH_2), 25.10 (CH_2), 21.29 (CH_3, olefinic-CH_3), 21.26 (CH_3, olefinic-CH_3), 14.1 (2 x CH_3, 2 x OCH_2CH_3); LRMS m/z 429.00 ($M + H^+$), calcd $C_{24}H_{28}O_7$ 428.1835; HRMS m/z 451.1730 (M + Na), calcd for $C_{24}H_{28}O_7Na$ 451.1733; Anal. calcd for $C_{24}H_{28}O_7$ (428.18): C, 67.28; H, 6.59. Found: C, 67.15; H, 6.65%.

2-Methyl-4-oxo-3-(3-phenyl-propenyl)-cyclohex-2-enecarboxylic acid ethyl ester (92ay): Prepared following the procedure **2e** and purified by column chromatography using EtOAc/hexane and isolated as a colorless oily liquid. IR (neat): ν_{max} 2923, 1728 (C=O), 1672 (O-C=O), 1158 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.30 (2H, t, *J* = 7.2 Hz), 7.23 (2H, d, *J* = 7.2 Hz), 7.20 (1H, t, *J* = 7.2 Hz), 6.26-6.05 (2H, m, olefinic-*H*), 4.20 (2H, q, *J* = 7.2 Hz, OCH_2CH_3), 3.52 (2H, d, *J* = 6.4 Hz), 3.35 (1H, t, *J* = 4.4 Hz), 2.66-2.57 (1H, m), 2.40 (1H, td, *J* = 16.8, 5.2 Hz), 2.30-2.15 (2H, m), 2.04 (3H, s, olefinic-CH_3), 1.28 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$) δ 197.2 (C, C=O), 172.0 (C, O-C=O), 150.3 (C), 140.0 (C), 136.1 (CH), 134.5 (C), 128.5 (2 x CH), 128.4 (2 x CH), 126.0 (CH), 123.4 (CH), 61.2 (CH_2, OCH_2CH_3), 48.0 (CH), 40.0 (CH_2), 35.2 (CH_2), 25.2 (CH_2), 21.5 (CH_3, olefinic-CH_3), 14.1 (CH_3, OCH_2CH_3); LRMS m/z 299.25 ($M + H^+$), calcd $C_{19}H_{22}O_3$ 298.1569; HRMS m/z 337.1846 (M + K), calcd for $C_{19}H_{22}O_3K$ 337.1206; Anal. calcd for $C_{19}H_{22}O_3$ (298.15): C, 76.48; H, 7.43. Found: C, 76.51; H, 7.38%.



92ay
E/*Z* = >99:1

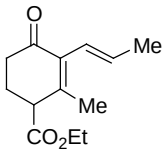
3-But-1-enyl-2-methyl-4-oxo-cyclohex-2-enecarboxylic acid ethyl ester (92az): Prepared following the procedure **2e** and purified by column



92az
E/*Z* = >99:1

chromatography using EtOAc/hexane and isolated as a colorless oily liquid. IR (neat): ν_{max} 2963, 2930, 1730 (C=O), 1674 (O-C=O), 1454, 1373, 1157, 1040, 970, 862, 779 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.07 (1H, d, *J* = 16.4 Hz), 5.97 (1H, td, *J* = 16.4, 6.4 Hz), 4.21 (2H, q, *J* = 7.2 Hz, OCH_2CH_3), 3.35 (1H, t, *J* = 4.4 Hz), 2.66-2.58 (1H, m), 2.40 (1H, td, *J* = 16.8, 5.2 Hz), 2.29-2.16 (4H, m), 2.06 (3H, s, olefinic-CH_3), 1.29 (3H, t, *J* = 7.2 Hz, OCH_2CH_3), 1.06 (3H, t, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$) δ 197.5 (C, C=O), 172.2 (C, O-C=O), 149.7 (C), 139.6 (CH), 134.9 (C), 121.1 (CH), 61.2 (CH_2, OCH_2CH_3), 48.1 (CH), 35.3 (CH_2), 26.7 (CH_2), 25.2 (CH_2), 21.5 (CH_3, olefinic-CH_3), 14.2 (CH_3, OCH_2CH_3), 13.5 (CH_3, CH_2CH_3); LRMS m/z 237.20 ($M + H^+$), calcd $C_{14}H_{20}O_3$ 236.1412; HRMS m/z 259.1308 (M + Na), calcd for $C_{14}H_{20}O_3Na$ 259.1310; Anal. calcd for $C_{14}H_{20}O_3$ (236.14): C, 71.16; H, 8.53. Found: C, 71.22; H, 8.45%.

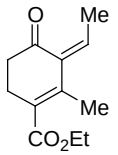
2-Methyl-4-oxo-3-propenyl-cyclohex-2-enecarboxylic acid ethyl ester (92aa'):



92aa'
E/*Z* = >99:1

Prepared following the procedure **2e** and purified by column chromatography using EtOAc/hexane and isolated as a yellow liquid. IR (neat): ν_{max} 2980, 2936, 2882, 1732 (C=O), 1674 (O-C=O), 1451, 1373, 1350, 1157, 1040, 860 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.09 (1H, d, *J* = 16.0 Hz), 5.95 (1H, qd, *J* = 15.6, 6.4 Hz), 4.21 (2H, q, *J* = 7.2 Hz, OCH_2CH_3), 3.35 (1H, t, *J* = 4.8 Hz), 2.66-2.57 (1H, m), 2.40 (1H, td, *J* = 16.8, 5.2 Hz), 2.30-2.16 (2H, m), 2.05 (3H, s, olefinic-CH_3), 1.84 (3H, dd, *J* = 6.4, 1.2 Hz, HC=CHCH_3), 1.29 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$) δ 197.4 (C, C=O), 172.1 (C, O-C=O), 149.7 (C), 134.8 (C), 132.7 (CH), 123.3 (CH), 61.2 (CH_2, OCH_2CH_3), 48.0 (CH), 35.2 (CH_2), 25.2 (CH_2), 21.4 (CH_3, olefinic-CH_3), 19.1 (CH_3), 14.1 (CH_3, OCH_2CH_3); LRMS m/z 223.15 ($M + H^+$), calcd $C_{13}H_{18}O_3$ 222.1256; HRMS m/z 245.1151 (M + Na), calcd for $C_{13}H_{18}O_3Na$ 245.1154; Anal. calcd for $C_{13}H_{18}O_3$ (222.12): C, 70.24; H, 8.16. Found: C, 70.12; H, 8.22%.

3-Ethylidene-2-methyl-4-oxo-cyclohex-1-enecarboxylic acid ethyl ester (89ab'):



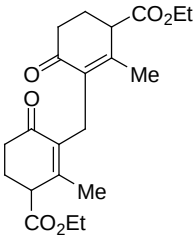
89ab'
E/*Z* = 1:>99

Prepared following the procedure **2e** and purified by column

chromatography using EtOAc/hexane and isolated as a colorless oily liquid. IR (neat): ν_{max} 2978, 1701 (C=O and O-C=O), 1241, 1184, 1069, 1021, 637 cm^{-1}; ^1H NMR ($CDCl_3$, 1:99 ratio of *E/Z* isomers) δ 6.44 (1H, q, *J* = 7.6 Hz, C=C*H*CH_3), 4.24 (2H, q, *J* = 7.2 Hz, OC*H*$_2$$CH_3$), 2.72 (2H, t, *J* = 6.8 Hz), 2.56 (2H, t, *J* = 6.8 Hz), 2.19 (3H, d, *J* = 7.6 Hz, C=CHC*H*$_3$), 2.14 (3H, s, olefinic-C*H*$_3$), 1.32 (3H, t, *J* = 7.2 Hz, OCH_2C*H*$_3$); ^{13}C NMR ($CDCl_3$, 1:99 ratio of *E/Z* isomers) δ 201.0 (C, C=O), 168.8 (C, O-C=O), 141.0 (C), 138.9 (CH, *C*HCH_3), 136.0 (C), 126.1 (C), 60.6 (CH_2, O*C*$H_2$$CH_3$), 39.3 ($CH_2$), 25.8 ($CH_2$), 16.7 ($CH_3$), 16.3 ($CH_3$), 14.3 ($CH_3$, OCH_2*C*H_3); LRMS m/z 209.15 (M + H^+), calcd $C_{12}H_{16}O_3$ 208.1099; HRMS m/z 247.0715 (M + K), calcd for $C_{12}H_{16}O_3K$ 247.0736; Anal. calcd for $C_{12}H_{16}O_3$ (208.10): C, 69.21; H, 7.74. Found: C, 69.32; H, 7.71%.

2f: Piperidine-catalyzed cascade Claisen-Schmidt and Michael reactions: In an ordinary glass vial equipped with a magnetic stirring bar, to 0.5 mmol of the Hagemann's ester **88** was added 1.5 mL of DMSO solvent, and then the catalyst piperidine **2b** (0.05 mmol, 4.93 µL) was added and then 0.25 mmol of formaldehyde **28c'** (37 wt% solution in water) was added in one-portion and the reaction mixture was stirred at 25 °C for the time indicated in Scheme 4. The crude reaction mixture was worked up with aqueous NH_4Cl solution and the aqueous layer was extracted with dichloromethane (2 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The pure cascade products **93** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Diethyl 3,3'-methylenebis(2-methyl-4-oxocyclohex-2-enecarboxylate) (93ac'):

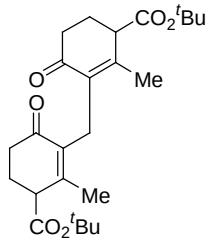


93ac'
dr: >99:1

Prepared following the procedure **2f** and purified by column chromatography using EtOAc/hexane and isolated as a colorless oily liquid. IR (neat): ν_{max} 2928, 2859, 1728 (C=O), 1667 (O-C=O), 1622, 1512, 1451, 1372, 1157, 1042 cm^{-1}; ^1H NMR ($CDCl_3$, >99:1 ratio of diastereomers) δ 4.18 (2H, q, *J* = 7.2 Hz, OC*H*$_2$$CH_3$), 4.17 (2H, q, *J* =

7.2 Hz, OCH_2CH$_3$), 3.44 (2H, d, *J* = 12.8 Hz), 3.28 (1H, t, *J* = 4.8 Hz), 3.27 (1H, t, *J* = 4.8 Hz), 2.59-2.50 (2H, m), 2.40-2.32 (2H, m), 2.26-2.13 (4H, m), 2.00 (3H, s, olefinic-CH_3), 1.95 (3H, s, olefinic-CH_3), 1.28 (3H, t, *J* = 7.2 Hz, OCH$_2$CH_3), 1.27 (3H, t, *J* = 7.2 Hz, OCH$_2$CH_3); ^{13}C NMR (CDCl$_3$, >99:1 ratio of diastereomers) δ 197.0 (C, C=O), 196.9 (C, C=O), 172.2 (C, O-C=O), 172.1 (C, O-C=O), 150.8 (C), 150.7 (C), 135.8 (C), 135.7 (C), 61.1 (2 x CH$_2$, O*C*H$_2$CH$_3$), 48.2 (CH), 48.1 (CH), 34.6 (CH$_2$), 25.5 (CH$_2$), 25.3 (CH$_2$), 22.3 (CH$_2$), 21.8 (CH$_2$), 21.0 (2 x CH$_3$, olefinic-*C*H$_3$), 14.1 (2 x CH$_3$, OCH$_2$*C*H$_3$); LRMS m/z 377.25 (M + H$^+$), calcd C$_{21}$H$_{28}$O$_6$ 376.1886; Anal. calcd for C$_{21}$H$_{28}$O$_6$ (376.18): C, 67.00; H, 7.50. Found: C, 67.49; H, 7.54%.

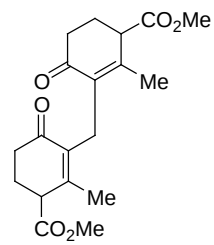
Di-*tert*-butyl-3,3'-methylenebis(2-methyl-4-oxocyclohex-2-enecarboxylate) (93bc'):



93bc'
dr: >99:1

Prepared following the procedure **2f** and purified by column chromatography using EtOAc/hexane and isolated as a colorless oily liquid. IR (neat): ν_{max} 2928, 2857, 1724 (C=O), 1671 (O-C=O), 1454, 1370, 1256, 1152, 847 cm^{-1}; ^{1}H NMR (CDCl$_3$, >99:1 ratio of diastereomers) δ 3.43 (2H, d, *J* = 15.6 Hz), 3.20-3.15 (2H, m), 2.61-2.50 (2H, m), 2.36-2.32 (2H, m), 2.23-2.08 (4H, m), 2.01 (3H, s, olefinic-CH_3), 1.95 (3H, s, olefinic-CH_3), 1.46 (9H, s, OC(CH_3)$_3$), 1.45 (9H, s, OC(CH_3)$_3$); ^{13}C NMR (CDCl$_3$, >99:1 ratio of diastereomers) δ 197.3 (C, C=O), 197.1 (C, C=O), 171.4 (C, O-C=O), 171.3 (C, O-C=O), 151.40 (C), 151.35 (C), 135.6 (C), 135.4 (C), 81.6 (2 x C, 2 x O*C*(CH$_3$)$_3$), 49.2 (2 x CH), 34.7 (CH$_2$), 28.0 (6 x CH$_3$, 2 x OC(*C*H$_3$)$_3$), 25.6 (CH$_2$), 25.4 (CH$_2$), 22.4 (CH$_2$), 21.7 (CH$_2$), 21.1 (CH$_3$, olefinic-*C*H$_3$), 21.0 (CH$_3$, olefinic-*C*H$_3$); LCMS m/z 431.45 (M – H$^+$), calcd C$_{25}$H$_{36}$O$_6$ 432.2512; Anal. calcd for C$_{25}$H$_{36}$O$_6$ (432.25): C, 69.42; H, 8.39. Found: C, 69.35; H, 8.41%.

Dimethyl-3,3'-methylenebis(2-methyl-4-oxocyclohex-2-enecarboxylate) (93sc'):



93sc'
dr: >99:1

Prepared following the procedure **2f** and purified by column chromatography using EtOAc/hexane and isolated as a colorless oily

liquid. IR (neat): ν_{max} 3052, 2957, 1732 (C=O), 1667 (O-C=O), 1622, 1435, 1346, 1271, 1161, 1078, 1042 cm^{-1}; ^1H NMR ($CDCl_3$, >99:1 ratio of diastereomers) δ 3.73 (6H, 2 x OC*H*$_3$), 3.45 (2H, br s), 3.31 (2H, t, *J* = 4.4 Hz), 2.57-2.48 (2H, m), 2.40-2.33 (2H, m), 2.26-2.13 (4H, m), 1.99 (3H, s, olefinic-C*H*$_3$), 1.95 (3H, s, olefinic-C*H*$_3$); ^{13}C NMR ($CDCl_3$, >99:1 ratio of diastereomers) δ 197.0 (C, C=O), 196.9 (C, C=O), 172.7 (C, O-C=O), 172.6 (C, O-C=O), 150.8 (C), 150.6 (C), 135.9 (C), 135.8 (C), 52.24 (CH_3, O*C*H$_3$), 52.21 (CH_3, O*C*H$_3$), 48.0 (CH), 47.9 (CH), 34.6 (CH_2), 25.5 (CH_2), 25.3 (CH_2), 22.2 (CH_2), 22.0 (CH_2), 21.0 (CH_3, olefinic-*C*H$_3$), 20.98 (CH_3, olefinic-*C*H$_3$); GCMS m/z 348.30 (M^+), calcd $C_{19}H_{24}O_6$ 348.1573; Anal. calcd for $C_{19}H_{24}O_6$ (348.15): C, 65.50; H, 6.94. Found: C, 65.63; H, 6.94%.

2g: Sequential combination of piperidine-catalyzed cascade Knoevenagel/Michael/aldol condensation/decarboxylation and (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine-catalyzed Claisen-Schmidt/iso-aromatization reactions in one-pot: To a stirred solution of ethyl acetoacetate (2.0 mmol) and aldehyde (1.0 mmol) in EtOH (2 mL) was added a catalytic amount of piperidine **2b** (0.35 mmol, 35 mol%) and the reaction mixture was stirred at 80 °C for 5-6 h. Solvent ethanol and piperidine was evaporated by vacuum pump then solvent DMSO (1 mL) was added and catalyst (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine **2i** (0.1 mmol, 16.3 µL), aldehyde **28** (0.5 mmol) were added and the reaction mixture was stirred at 25 °C for 13-24 h. The crude reaction mixture was worked up with aqueous NH_4Cl solution and the aqueous layer was extracted with dichloromethane (2 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure one-pot products **90** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Base–induced iso-aromatization of 3-arylidene-Hagemann's esters:

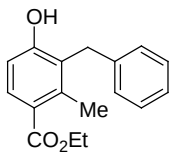
2h: Synthesis of 90aa: In an ordinary glass vial equipped with a magnetic stirring bar, to 0.3 mmol of the 2-methyl-3-(4-nitro-benzylidene)-4-oxo-cyclohex-1-enecarboxylic acid ethyl ester **89aa** was added 0.6 mL of DMSO solvent, and then the catalyst (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine **2i** (0.06 mmol, 9.7µL) was added and

the reaction mixture was stirred at 25 °C for 0.5 hour as indicated in Scheme 5. The crude reaction mixture was worked up with aqueous NH_4Cl solution and the aqueous layer was extracted with dichloromethane (2 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure cascade product **90aa** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

2i: Synthesis of 90ab: In an ordinary glass vial equipped with a magnetic stirring bar, to 0.18 mmol of the 3-benzylidene-2-methyl-4-oxo-cyclohex-1-enecarboxylic acid ethyl ester **89ab** was added 0.36 mL of DMSO solvent, and then the catalyst piperidine **2b** (0.036 mmol, 3.55 µL) was added and the reaction mixture was stirred at 70 °C for 12 hours as indicated in Scheme 5. The crude reaction mixture was worked up with aqueous NH_4Cl solution and the aqueous layer was extracted with dichloromethane (2 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The pure cascade product **90ab** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

2j: Synthesis of 90ab and 90mb: In an ordinary glass vial equipped with a magnetic stirring bar, to 1.0 mmol of the Hagemann's ester **88a** or **88m** was added 1.0 mL of DMSO solvent, and then the catalyst piperidine **2b** (0.1 mmol, 9.87 µL) was added and then 0.5 mmol of benzaldehyde **28b** was added in one-portion and the reaction mixture was stirred at 70 °C for 18 hours as indicated in Scheme 5. The crude reaction mixture was worked up with aqueous NH_4Cl solution and the aqueous layer was extracted with dichloromethane (2 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The pure cascade products **90ab** and **90mb** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

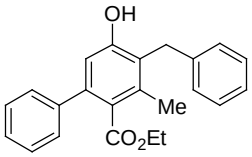
3-Benzyl-4-hydroxy-2-methyl-benzoic acid ethyl ester (90ab): Prepared following the procedure **2j** and purified by column chromatography using EtOAc/hexane and isolated as a white solid. Mp 102 °C; IR (neat): ν_{max} 3362 (O-*H*), 2920, 2851, 1680 (O-C=O), 1638, 1580, 1454, 1267, 1177, 1051, 696 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.70 (1H, d, *J* = 8.4 Hz), 7.23 (2H,



90ab

t, *J* = 6.8 Hz), 7.16 (1H, t, *J* = 6.8 Hz), 7.11 (2H, d, *J* = 7.2 Hz), 6.72 (1H, d, *J* = 8.4 Hz); 6.00 (1H, s, O-*H*), 4.31 (2H, q, *J* = 7.2 Hz, OCH_2CH$_3$), 4.11 (2H, s, CH_2Ar), 2.48 (3H, s, Ar-CH_3), 1.36 (3H, t, *J* = 7.2 Hz, OCH$_2$CH_3); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 168.6 (C, O-C=O), 157.1 (C), 141.1 (C), 139.5 (C), 130.4 (CH), 128.4 (2 x CH), 128.0 (2 x CH), 126.4 (C), 126.0 (CH), 123.6 (C), 112.6 (CH), 60.7 (CH$_2$, OCH$_2$CH$_3$), 31.6 (CH$_2$, CH$_2$Ar), 17.0 (CH$_3$, Ar-CH$_3$), 14.3 (CH$_3$, OCH$_2$CH$_3$); LRMS m/z 271.00 (M + H$^+$), calcd C$_{17}$H$_{18}$O$_3$ 270.1256; Anal. calcd for C$_{17}$H$_{18}$O$_3$ (270.12): C, 75.53; H, 6.71. Found: C, 75.62; H, 6.68%.

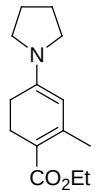
4-Benzyl-5-hydroxy-3-methyl-biphenyl-2-carboxylic acid ethyl ester (90mb):



90mb

Prepared following the procedure **2j** and purified by column chromatography using EtOAc/hexane and isolated as a yellow liquid; IR (neat): ν$_{max}$ 3403 (O-*H*), 2986, 2926, 1694 (O-C=O), 1589, 1452, 1263, 1173, 1053 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.35 (5H, br s), 7.30-7.27 (3H, m), 7.21-7.19 (3H, m); 6.68 (1H, br s, O-*H*), 4.11 (2H, s, CH_2Ar), 4.01 (2H, q, *J* = 7.2 Hz, OCH_2CH$_3$), 2.30 (3H, s, Ar-CH_3), 0.92 (3H, t, *J* = 7.2 Hz, OCH$_2$CH_3); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 170.4 (C, O-C=O), 154.5 (C), 140.7 (C), 139.9 (C), 139.2 (C), 136.4 (C), 128.5 (2 x CH), 128.2 (6 x CH), 127.3 (CH), 127.1 (C), 126.1 (CH), 124.8 (C), 114.4 (CH), 61.0 (CH$_2$, OCH$_2$CH$_3$), 31.7 (CH$_2$, CH$_2$Ar), 16.8 (CH$_3$, Ar-CH$_3$), 13.6 (CH$_3$, OCH$_2$CH$_3$); LRMS m/z 347.00 (M + H$^+$), calcd C$_{23}$H$_{22}$O$_3$ 346.1569; HRMS m/z 369.1466 (M + Na), calcd for C$_{23}$H$_{22}$O$_3$Na 369.1467; Anal. calcd for C$_{23}$H$_{22}$O$_3$ (346.15): C, 79.74; H, 6.40. Found: C, 79.65; H, 6.47%.

2-Methyl-4-pyrrolidin-1-yl-cyclohexa-1,3-dienecarboxylic acid ethyl ester (95):



95

This product was prepared in NMR tube as DMSO-D$_6$ solvent. IR (neat): ν$_{max}$ 1662, 1514, 1278, 1205, 1028, 823, 761 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 4.52 (1H, s, olefinic-*H*), 4.00 (2H, q, *J* = 7.2 Hz, CO$_2$CH_2CH$_3$), 3.24 (4H, m, 2 x CH_2), 2.40 (2H, br t, *J* = 8.8 Hz, CH_2), 2.30 (2H, br t, *J* = 8.8 Hz, CH_2), 2.12 (3H, s, olefinic-CH_3), 1.85 (4H, m, 2 x CH_2), 1.18 (3H, t, *J* = 7.2 Hz, CO$_2$CH$_2$CH_3); ^{13}C NMR (CDCl$_3$) δ 167.1 (C, O-C=O), 152.5 (C), 150.3 (C), 103.6 (C), 96.7 (CH),

58.0 (CH_2), 47.0 (CH_2), 46.3 (CH_2), 26.4 (CH_2), 25.1 (CH_2), 24.6 (CH_2), 23.7 (CH_2), 22.1 (CH_3), 14.5 (CH_3); GCMS m/z 235.10 (M^+), calcd $C_{14}H_{21}NO_2$ 235.1572.

1-(4-Ethoxycarbonyl-3-methyl-cyclohexa-1,3-dienyl)-pyrrolidine-2-carboxylic acid (103): This product was prepared *in situ* in NMR tube and DMSO-D_6 as solvent. IR (neat): ν_{max} 3416 (COOH), 2257, 2130, 1651 (O-C=O), 1377, 1026, 999, 826 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.54 (1H, s, olefinic-*H*), 4.34-4.24 (1H, m), 4.01 (2H, q, *J* = 7.2 Hz, OCH_2CH_3), 3.40-3.32 (2H, m), 2.43-2.26 (4H, m), 2.19-2.14 (2H, m), 2.10 (3H, s, olefinic-CH_3), 1.92-1.85 (2H, m), 1.18 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$) δ 174.3 (C, O-C=O), 167.3 (C, COOH), 152.0 (C), 149.8 (C), 105.2 (C), 98.0 (CH), 60.1 (CH), 58.4 (CH_2, OCH_2CH_3), 47.9 (CH_2), 30.1 (CH_2), 26.3 (CH_2), 23.9 (CH_2), 23.1 (CH_2), 22.2 (CH_3, olefinic-CH_3), 14.6 (CH_3, OCH_2CH_3); LRMS m/z 278.00 ($M - H^+$), calcd $C_{15}H_{21}NO_4$ 279.1471.

103

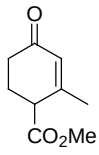
3: General experimental procedures for the Hagemann's esters synthesis:

3a: ^{t}BuOK-Catalyzed cascade Knoevenagel/Michael/aldol condensation/decarboxylation reactions: To a stirred solution of β-keto ester (2 equiv.) and aldehyde (1 equiv.) in *t*-BuOH (1 M) was added a catalytic amount of ^{t}BuOK (0.10 equiv.) at 0 °C. The reaction mixture was stirred at that temperature for 60 min, and 0.25 equiv. of *t*-BuOK was added again. The mixture was then heated at reflux for 32-40 h. Upon cooling to room temperature, the mixture was quenched with 1 M HCl (10 mL) solution, diluted with dichloromethane (50 mL), washed with 1 M NaOH solution (20 mL) and brine (20 mL). The separated organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Pure cascade products **88a-b**,**88i-s** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

3b: Piperidine-catalyzed cascade Knoevenagel/Michael/aldol condensation/decarboxylation reactions: To a stirred solution of β-keto ester (4 mmol) and benzaldehyde (2 mmol) in EtOH (4 mL) was added a catalytic amount of piperidine (0.7 mmol, 35 mol%) and the reaction mixture was stirred at 80 °C for 3 h.

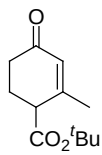
Upon cooling to room temperature, the mixture was quenched with aqueous NH_4Cl solution, diluted with diethyl ether (50 mL), washed with brine (10 mL). The separated organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Pure cascade products **88j** and **88m-r** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

2-Methyl-4-oxo-cyclohex-2-enecarboxylic acid methyl ester (88s): Purified by column chromatography using EtOAc/hexane and isolated as a liquid. IR (neat): ν_{max} 2955, 1734 (O-C=O), 1670 (C=O), 1251, 1199, 1033, 779 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.96 (1H, s, olefinic-*H*), 3.76 (3H, s, OCH_3), 3.30 (1H, t, *J* = 4.8 Hz), 2.55 (1H, m), 2.38 (2H, m), 2.23 (1H, m), 2.03 (3H, s, olefinic-CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 198.1 (C, C=O), 171.9 (C, O-C=O), 156.8 (C), 128.4 (CH), 52.4 (CH_3, O*C*H_3), 45.8 (CH), 34.2 (CH_2), 26.0 (CH_2), 23.4 (CH_3, olefinic-*C*H_3).



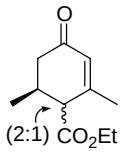
88s

2-Methyl-4-oxo-cyclohex-2-enecarboxylic acid *tert*-butyl ester (88b): Purified by column chromatography using EtOAc/hexane and isolated as a liquid. IR (neat): ν_{max} 2978, 1718 (O-C=O), 1676 (C=O), 1454, 1369, 1251, 1151, 844 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.94 (1H, s, olefinic-*H*), 3.16 (1H, t, *J* = 5.2 Hz), 2.56 (1H, m), 2.30 (2H, m), 2.17 (1H, m), 2.02 (3H, s, olefinic-CH_3), 1.43 (9H, s, OC(CH_3)$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 198.5 (C, C=O), 170.7 (C, O-C=O), 157.6 (C), 128.1 (CH), 81.9 (C, O*C*(CH_3)$_3$), 47.1 (CH), 34.3 (CH_2), 28.0 (CH_3, OC(*C*H_3)$_3$), 26.2 (CH_2), 23.5 (CH_3, olefinic-*C*H_3).

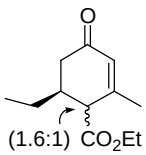


88b

2,6-Dimethyl-4-oxo-cyclohex-2-enecarboxylic acid ethyl ester (88i): Purified by column chromatography using EtOAc/hexane and isolated as a light yellow oil. IR (neat): ν_{max} 2962, 1730 (O-C=O), 1668 (C=O), 1192, 1028, 910, 854, 756 cm^{-1}; ^1H NMR ($CDCl_3$, 2.0:1 ratio of diastereomers, major isomer) δ 5.97 (1H, s, olefinic-*H*), 4.24 (2H, q, *J* = 7.2 Hz, OCH_2CH$_3$), 3.03 (1H, d, *J* = 7.2 Hz), 2.59 (2H, m), 2.12 (1H, m), 1.97 (3H, s, olefinic-CH_3), 1.31



88i

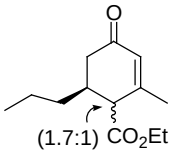


88j

(3H, t, *J* = 7.6 Hz, OCH_2CH_3), 1.10 (3H, d, *J* = 6.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, 2.0:1 ratio of diastereomers, major isomer) δ 197.9 (C, C=O), 171.8 (C, O-C=O), 155.8 (C), 127.9 (CH), 61.1 (CH_2, OCH_2CH_3), 54.4 (CH), 43.0 (CH_2), 32.7 (CH), 22.6 (CH_3, olefinic-CH_3), 19.7 (CH_3, $CHCH_3$), 14.1 (CH_3, OCH_2CH_3).

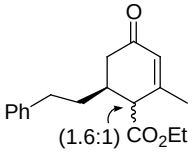
6-Ethyl-2-methyl-4-oxo-cyclohex-2-enecarboxylic acid ethyl ester (88j): Purified by column chromatography using EtOAc/hexane and isolated as a liquid. IR (neat): ν_{max} 2972, 1734 (O-C=O), 1672 (C=O), 1186, 1030, 758, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 1.6:1 ratio of diastereomers, major isomer) δ 5.95 (1H, s, olefinic-*H*), 4.20 (2H, q, *J* = 7.2 Hz, OCH_2CH_3), 3.13 (1H, d, *J* = 6.4 Hz), 2.62 (2H, m), 2.12 (1H, m), 1.97 (3H, s, olefinic-CH_3), 1.48 (2H, m), 1.31 (3H, t, *J* = 7.2 Hz, OCH_2CH_3), 0.93 (3H, t, *J* = 7.2 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135, 1.6:1 ratio of diastereomers, major isomer) δ 198.1 (C, C=O), 171.9 (C, O-C=O), 155.8 (C), 127.9 (CH), 61.2 (CH_2, OCH_2CH_3), 52.3 (CH), 39.9 (CH_2), 39.1 (CH), 26.4 (CH_2), 22.8 (CH_3, olefinic-CH_3), 14.1 (CH_3, OCH_2CH_3), 10.9 (CH_3, CH_2CH_3).

2-Methyl-4-oxo-6-propyl-cyclohex-2-enecarboxylic acid ethyl ester (88k): Purified by column chromatography using EtOAc/hexane and isolated as a liquid. IR (neat): ν_{max} 2961, 1732 (O-C=O), 1674 (C=O), 1186, 1026 cm^{-1}; ^1H NMR ($CDCl_3$, 1.7:1 ratio of diastereomers, major isomer) δ 5.96 (1H, s, olefinic-*H*), 4.22 (2H, q, *J* = 7.2 Hz, OCH_2CH_3), 3.10 (1H, d, *J* = 6.8 Hz), 2.61 (2H, m), 2.34 (1H, m), 1.97 (3H, s, olefinic-CH_3), 1.50-1.20 (4H, m), 1.29 (3H, t, *J* = 7.2 Hz, OCH_2CH_3), 0.91 (3H, t, *J* = 7.2 Hz, $CH_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$, DEPT-135, 1.7:1 ratio of diastereomers, major isomer) δ 198.1 (C, C=O), 171.8 (C, O-C=O), 155.8 (C), 128.0 (CH), 61.2 (CH_2, OCH_2CH_3), 52.7 (CH), 40.1 (CH_2), 37.2 (CH), 35.7 (CH_2), 22.9 (CH_3, olefinic-CH_3), 19.6 (CH_2), 14.1 (CH_3, OCH_2CH_3), 13.8 (CH_3, $CH_2CH_2CH_3$).



88k

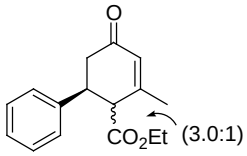
2-Methyl-4-oxo-6-phenethyl-cyclohex-2-enecarboxylic acid ethyl ester (88l): Purified by column chromatography using EtOAc/hexane and isolated as a liquid. IR (neat): ν_{max} 3024, 2932, 2862, 1732 (O-C=O), 1670



88l

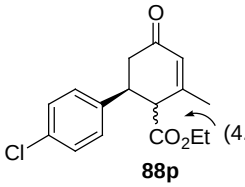
(C=O), 1496, 1454, 1259, 1170, 1030, 750, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 1.6:1 ratio of diastereomers, major isomer) δ 7.28-7.13 (5H, m, Ph-*H*), 5.96 (1H, s, olefinic-*H*), 4.20 (2H, q, *J* = 7.2 Hz, OCH_2CH$_3$), 3.14 (1H, d, *J* = 6.4 Hz), 2.69 (2H, m), 2.53 (2H, m), 2.29 (1H, m), 1.95 (3H, s, olefinic-CH_3), 1.72 (2H, m), 1.28 (3H, t, *J* = 6.8 Hz, OCH$_2$CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135, 1.6:1 ratio of diastereomers, major isomer) δ 197.6 (C, C=O), 171.5 (C, O-C=O), 155.6 (C), 141.1 (C), 128.4 (2 x CH), 128.3 (2 x CH), 128.0 (CH), 125.9 (CH), 61.3 (CH_2, OCH_2CH$_3$), 52.6 (CH), 40.1 (CH_2), 37.0 (CH), 35.4 (CH_2), 32.8 (CH_2), 23.0 (CH_3, olefinic-*C*H$_3$), 14.2 (CH_3, OCH$_2$*C*H$_3$).

2-Methyl-4-oxo-6-phenyl-cyclohex-2-enecarboxylic acid ethyl ester (88m): Purified by column chromatography using EtOAc/hexane and isolated as a liquid. IR (neat): ν_{max} 3032, 2982, 1732 (O-C=O), 1670 (C=O), 1496, 1454, 1180, 1032, 760, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 3.0:1 ratio of diastereomers, major isomer) δ 7.36-7.20 (5H, m, Ph-*H*), 6.06 (1H, s, olefinic-*H*), 4.05 (2H, q, *J* = 7.2 Hz, OCH_2CH$_3$), 3.64 (1H, m), 3.48 (1H, m), 2.68 (2H, m), 2.01 (3H, s, olefinic-CH_3), 1.14 (3H, t, *J* = 7.2 Hz, OCH$_2$CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135, 3.0:1 ratio of diastereomers, major isomer) δ 197.2 (C, C=O), 171.2 (C, O-C=O), 156.2 (C), 140.9 (C), 128.7 (2 x CH), 128.4 (CH), 127.4 (CH), 127.2 (2 x CH), 61.1 (CH_2, OCH_2CH$_3$), 54.3 (CH), 44.1 (CH), 42.8 (CH_2), 22.4 (CH_3, olefinic-*C*H$_3$), 13.9 (CH_3, OCH$_2$*C*H$_3$).

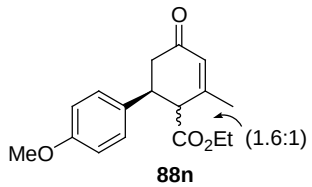


88m

6-(4-Chloro-phenyl)-2-methyl-4-oxo-cyclohex-2-enecarboxylic acid ethyl ester (88p): Purified by column chromatography using EtOAc/hexane and isolated as a solid. IR (neat): ν_{max} 2980, 1734 (O-C=O), 1674 (C=O), 1493, 1014, 736 cm^{-1}; ^1H NMR ($CDCl_3$, 4.8:1 ratio of diastereomers, major isomer) δ 7.29 (2H, d, *J* = 7.2 Hz), 7.17 (2H, d, *J* = 7.2 Hz), 6.06 (1H, s, olefinic-*H*), 4.07 (2H, q, *J* = 7.2 Hz, OCH_2CH$_3$), 3.64 (1H, m), 3.53 (1H, m), 2.67 (2H, m), 1.98 (3H, s, olefinic-CH_3), 1.12 (3H, t, *J* = 7.2 Hz, OCH$_2$CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135, 4.8:1 ratio of diastereomers, major isomer) δ 196.7 (C, C=O), 171.0 (C, O-C=O), 156.0 (C), 139.3



88p

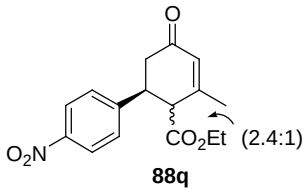


88n

(C), 133.1 (C), 128.9 (2 x CH), 128.6 (2 x CH), 128.4 (CH), 61.3 (CH_2, O*C*$H_2$$CH_3$), 54.1 (CH), 43.3 (CH), 42.6 (CH_2), 22.3 (CH_3, olefinic-*C*H_3), 13.9 (CH_3, OCH_2*C*H_3).

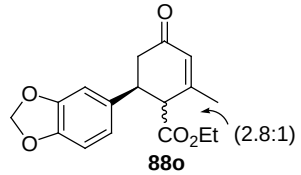
6-(4-Methoxy-phenyl)-2-methyl-4-oxo-cyclohex-2-enecarboxylic acid ethyl ester (88n): Purified by column chromatography using EtOAc/hexane and isolated as a gummy solid. IR (neat): ν_{max} 2980, 2837, 1734 (O-C=O), 1672 (C=O), 1612, 1514, 1458, 1258, 1033, 769, 734 cm^{-1}; ^1H NMR ($CDCl_3$, 2.8:1 ratio of diastereomers, major isomer) δ 7.14 (2H, d, *J* = 7.2 Hz), 6.85 (2H, d, *J* = 7.2 Hz), 6.05 (1H, s, olefinic-*H*), 4.07 (2H, q, *J* = 7.2 Hz, OC*H*$_2$$CH_3$), 3.79 ($CH_3$, s, OC*H*$_3$), 3.62 (1H, m), 3.53 (1H, m), 2.67 (2H, m), 1.98 (3H, s, olefinic-C*H*$_3$), 1.11 (3H, t, *J* = 7.2 Hz, OCH_2C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135, 2.8:1 ratio of diastereomers, major isomer) δ 197.5 (C, C=O), 171.4 (C, O-C=O), 158.8 (C), 156.3 (C), 133.0 (C), 128.4 (CH), 128.2 (2 x CH), 114.1 (2 x CH), 61.1 (CH_2, O*CH*$_2$$CH_3$), 55.4 ($CH_3$, O*CH*$_3$), 54.7 (CH), 43.3 (CH), 43.1 (CH_2), 22.3 (CH_3, olefinic-*C*H_3), 14.0 (CH_3, OCH_2*C*H_3).

2-Methyl-6-(4-nitro-phenyl)-4-oxo-cyclohex-2-enecarboxylic acid ethyl ester (88q):



88q

Purified by column chromatography using EtOAc/hexane and isolated as a gummy solid. IR (neat): ν_{max} 2982, 1736 (O-C=O), 1668 (C=O), 1601, 1521, 1033, 746, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 2.4:1 ratio of diastereomers, major isomer) δ 8.13 (2H, d, *J* = 7.2 Hz), 7.45 (2H, d, *J* = 7.2 Hz), 6.09 (1H, s, olefinic-*H*), 4.11 (2H, q, *J* = 7.6 Hz, OC*H*$_2$$CH_3$), 3.87 (1H, m), 3.61 (1H, m), 2.70 (2H, m), 2.02 (3H, s, olefinic-C*H*$_3$), 1.11 (3H, t, *J* = 7.2 Hz, OCH_2C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135, 2.4:1 ratio of diastereomers, major isomer) δ 195.9 (C, C=O), 170.7 (C, O-C=O), 155.7 (C), 148.3 (C), 147.5 (C), 128.5 (CH), 128.3 (2 x CH), 124.1 (2 x CH), 61.6 (CH_2, O*CH*$_2$$CH_3$), 53.6 (CH), 43.7 (CH), 42.1 (CH_2), 22.4 (CH_3, olefinic-*CH*$_3$), 14.0 (CH_3, OCH_2*CH*$_3$).

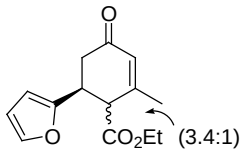


88o

6-Benzo[1,3]dioxol-5-yl-2-methyl-4-oxo-cyclohex-2-enecarboxylic acid ethyl ester (88o): Purified by column chromatography using EtOAc/hexane and isolated as a liquid. IR (neat): ν_{max} 2986, 2910, 1730 (O-C=O), 1670 (C=O), 1506, 1037, 933 cm^{-1}; ^1H NMR ($CDCl_3$, 2.8:1 ratio of diastereomers, major isomer) δ

6.78-6.65 (3H, m, Ph-*H*), 6.04 (1H, s, olefinic-*H*), 5.94 (2H, s, OCH_2O), 4.10 (2H, q, *J* = 7.2 Hz, OCH_2CH$_3$), 3.58 (1H, m), 3.43 (1H, m), 2.63 (2H, m), 1.98 (3H, s, olefinic-CH_3), 1.14 (3H, t, *J* = 7.2 Hz, OCH$_2$CH_3); ^{13}C NMR (CDCl$_3$, DEPT-135, 2.8:1 ratio of diastereomers, major isomer) δ 197.1 (C, C=O), 171.2 (C, O-C=O), 156.1 (C), 147.8 (C), 146.7 (C), 134.7 (C), 128.4 (CH), 120.5 (CH), 108.3 (CH), 107.4 (CH), 101.1 (CH$_2$, OCH$_2$O), 61.2 (CH$_2$, OCH_2CH$_3$), 54.6 (CH), 43.8 (CH), 43.1 (CH$_2$), 22.3 (CH$_3$, olefinic-CH$_3$), 14.1 (CH$_3$, OCH$_2$$CH_3$).

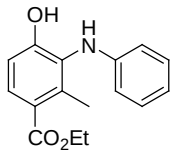
6-Furan-2-yl-2-methyl-4-oxo-cyclohex-2-enecarboxylic acid ethyl ester (88r):



88r

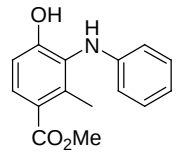
Purified by column chromatography using EtOAc/hexane and isolated as a gummy solid. IR (neat): ν_{max} 3119, 2982, 1732 (O-C=O), 1676 (C=O), 1504, 1440, 1186, 1016, 738 cm^{-1}; ^{1}H NMR (CDCl$_3$, 3.4:1 ratio of diastereomers, major isomer) δ 7.29 (1H, br s), 6.26 (1H, m), 6.04 (1H, m), 5.98 (1H, s, olefinic-*H*), 4.20 (2H, q, *J* = 7.2 Hz, OCH_2CH$_3$), 3.83 (1H, m), 3.63 (1H, m), 2.75 (2H, m), 1.98 (3H, s, olefinic-CH_3), 1.25 (3H, t, *J* = 7.2 Hz, OCH$_2$CH_3); ^{13}C NMR (CDCl$_3$, DEPT-135, 3.4:1 ratio of diastereomers, major isomer) δ 196.5 (C, C=O), 170.8 (C, O-C=O), 155.1 (C), 154.2 (C), 141.7 (CH), 128.1 (CH), 110.1 (CH), 106.0 (CH), 61.4 (CH$_2$, OCH_2CH$_3$), 51.0 (CH), 38.9 (CH$_2$), 37.0 (CH), 23.0 (CH$_3$, olefinic-CH$_3$), 14.1 (CH$_3$, OCH$_2$$CH_3$).

4a: Pyrrolidine and auto-catalyzed two-component cascade enamine amination/iso-aromatization reactions: In an ordinary glass vial equipped with a magnetic stirring bar, to 0.6 mmol of the Hagemann's esters **88** was added 1.0 mL of solvent, and then the catalyst pyrrolidine **2a** (0.015 mmol, 2.5 μL) was added and the reaction mixture was stirred at 25 °C for the 0.5 h; then 0.3 mmol of nitrosobenzene **56** was added in one-portion and the reaction mixture was stirred at 25 °C for the time indicated in Tables 11 and 13. The crude reaction mixture was directly loaded on silica gel column with or without aqueous work-up and pure cascade products **106** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

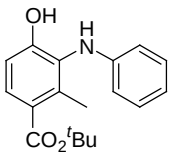

106aa

4-Hydroxy-2-methyl-3-phenylamino-benzoic acid ethyl ester (106aa): Purified by column chromatography using EtOAc/hexane and isolated as a light yellow solid. Mp 112 °C; IR (neat): ν_{max} 3400 (O-*H* and N-*H)*, 2926, 1668 (O-C=O), 1601, 1496, 1342, 1055, 748 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.88 (1H, d, *J* = 8.4 Hz), 7.19 (2H, t, *J* = 8.0 Hz), 6.92 (1H, d, *J* = 8.8 Hz), 6.85 (1H, t, *J* = 7.2 Hz), 6.58 (2H, d, *J* = 8.0 Hz), 5.01 (1H, s, N-*H*), 4.31 (2H, q, *J* = 6.8 Hz, O*C*$H_2$$CH_3$), 2.40 (3H, s, Ar-*C*$H_3$), 1.37 (3H, t, *J* = 6.8 Hz, OCH_2*C*H_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.3 (C, O-C=O), 157.3 (C), 145.7 (C), 140.4 (C), 131.4 (CH), 129.6 (2 x CH), 126.8 (C), 123.0 (C), 120.1 (CH), 114.1 (2 x CH), 111.8 (CH), 60.6 (CH_2, O*C*$H_2$$CH_3$), 15.6 ($CH_3$, Ar-*C*$H_3$), 14.3 ($CH_3$, OCH_2*C*H_3); LRMS m/z 270.10 ($M - H^+$), calcd $C_{16}H_{17}NO_3$ 271.1208; HRMS m/z 272.1271 (M +□ H^+), calcd $C_{16}H_{17}NO_3H^+$ 272.1286; Anal. calcd for $C_{16}H_{17}NO_3$ (271.12): C, 70.83; H, 6.32; N, 5.16. Found: C, 70.773; H, 6.342; N, 5.329%.

4-Hydroxy-2-methyl-3-phenylamino-benzoic acid methyl ester (106sa): Purified by column chromatography using EtOAc/hexane and isolated as a colorless liquid. IR (neat): ν_{max} 3362 (O-*H* and N-*H*), 3049, 2951, 1699 (O-C=O), 1601, 1496, 1435, 1055, 750, 692 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.89 (1H, d, *J* = 8.8 Hz), 7.12 (2H, t, *J* = 7.6 Hz), 6.93 (1H, d, *J* = 8.8 Hz), 6.86 (1H, t, *J* = 7.2 Hz), 6.83 (1H, s, O-*H*), 6.58 (2H, d, *J* = 8.0 Hz), 4.99 (1H, s, N-*H*), 3.86 (3H, s, O*C*H_3), 2.42 (3H, s, Ar-*CH*$_3$*)*; ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.6 (C, O-C=O), 157.4 (C), 145.7 (C), 140.6 (C), 131.5 (CH), 129.6 (2 x CH), 126.8 (C), 122.6 (C), 120.2 (CH), 114.2 (2 x CH), 111.8 (CH), 51.7 (CH_3, O*C*H_3), 15.6 (CH_3, Ar-*C*H_3); LRMS m/z 258.15 ($M + H^+$), calcd for $C_{15}H_{15}NO_3$ 257.1052; HRMS m/z 258.1125 ($M + H^+$), calcd for $C_{15}H_{15}NO_3H^+$ 258.1130.

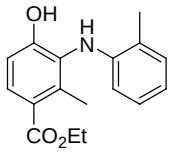

106sa

4-Hydroxy-2-methyl-3-phenylamino-benzoic acid tert-butyl ester (106ba): Purified by column chromatography using EtOAc/hexane and isolated as yellow oil. IR (neat): ν_{max} 3366 (O-*H* and N-*H*), 2978, 1699 (O-C=O), 1601, 1496, 1397, 1140, 1049, 750, 692 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.80 (1H,


106ba

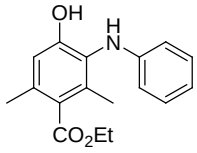
d, *J* = 8.8 Hz), 7.19 (2H, t, *J* = 8.0 Hz), 6.90 (1H, d, *J* = 8.4 Hz), 6.85 (1H, t, *J* = 7.6 Hz), 6.75 (1H, s, O-*H*), 6.58 (2H, d, *J* = 8.4 Hz), 4.98 (1H, s, N-*H*), 2.38 (3H, s, Ar-CH_3), 1.57 (9H, s, 3 x CH_3, tert-CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 166.7 (C, O-C=O), 156.9 (C), 145.7 (C), 139.7 (C), 131.3 (CH), 129.6 (2 x CH), 126.6 (C), 124.8 (C), 120.1 (CH), 114.2 (2 x CH), 111.7 (CH), 80.8 (C, O-*C*(CH_3)$_3$), 28.3 (3 x CH_3, O-C(*C*H_3)$_3$), 15.7 (CH_3, Ar-*C*H_3); LRMS m/z 300.30 (M + H^+), calcd for $C_{18}H_{21}NO_3$ 299.1521; HRMS m/z 300.1599 (M + H^+), calcd for $C_{18}H_{21}NO_3H^+$ 300.1599.

4-Hydroxy-2-methyl-3-o-tolylamino-benzoic acid ethyl ester (106ab): Purified by column chromatography using EtOAc/hexane and isolated as a yellow solid. Mp 96 °C; IR (neat): ν_{max} 3271 (O-*H* and N-*H*), 2926, 1670 (O-C=O), 1606, 1575, 1510, 1109, 1062, 746, 625 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.90 (1H, d, *J* = 8.8 Hz), 7.16 (1H, d, *J* = 7.6 Hz), 6.99 (1H, t, *J* = 7.6 Hz), 6.94 (1H, d, *J* = 8.8 Hz), 6.81 (1H, t, *J* = 7.2 Hz), 6.72 (1H, s, O-*H*), 6.18 (1H, d, *J* = 8.0 Hz), 4.83 (1H, s, N-*H*), 4.32 (2H, q, *J* = 7.2 Hz, OCH_2CH$_3$), 2.39 (3H, s, Ar-CH_3), 2.37 (3H, s, Ar-CH_3), 1.38 (3H, t, *J* = 7.2 Hz, OCH$_2$CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.2 (C, O-C=O), 157.2 (C), 143.5 (C), 140.0 (C), 131.4 (CH), 130.6 (CH), 127.4 (CH), 127.0 (C), 123.0 (C), 122.8 (C), 119.9 (CH), 112.2 (CH), 111.8 (CH), 60.6 (CH_2, O*C*H_2CH$_3$), 17.6 (CH_3, Ar-CH_3), 15.5 (CH_3, Ar-*C*H_3), 14.4 (CH_3, OCH$_2$CH_3); LRMS m/z 286.30 (M + H^+), calcd $C_{17}H_{19}NO_3$ 285.1365; HRMS m/z 286.1442 (M + H^+), calcd $C_{17}H_{19}NO_3H^+$ 286.1443.



106ab

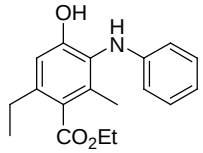
4-Hydroxy-2,6-dimethyl-3-phenylamino-benzoic acid ethyl ester (106ia): Purified by column chromatography using EtOAc/hexane and isolated as a light yellow solid. Mp 92 °C; IR (neat): ν_{max} 3368 (O-*H* and N-*H*), 2962, 1718 (O-C=O), 1602, 1496, 1369, 1043, 750, 694 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.19 (2H, t, *J* = 8.0 Hz), 6.84 (1H, t, *J* = 7.2 Hz), 6.76 (1H, s), 6.59 (2H, d, *J* = 8.0 Hz), 6.41 (1H, s, O-*H*), 4.88(1H, s, N-*H*), 4.36 (2H, q, *J* = 7.2 Hz, OCH_2CH$_3$), 2.32 (3H, s, Ar-CH_3), 2.10 (3H, s, Ar-CH_3), 1.37 (3H, t, *J* = 6.8 Hz, OCH$_2$CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 169.6 (C, O-C=O), 154.8 (C), 145.9 (C), 135.9 (C), 134.9 (C), 129.6 (2 x CH), 127.1 (C), 123.8 (C), 119.9 (CH),



106ia

114.1 (2 x CH), 114.0 (CH), 61.0 (CH_2, O*C*H_2CH$_3$), 20.0 (CH_3, Ar-CH_3), 15.2 (CH_3, Ar-*C*H_3), 14.3 (CH_3, OCH$_2$C*H*$_3$); LRMS m/z 286.20 (M + H^+), calcd $C_{17}H_{19}NO_3$ 285.1365; HRMS m/z 286.1425 (M + H^+), calcd $C_{17}H_{19}NO_3H^+$ 286.1443.

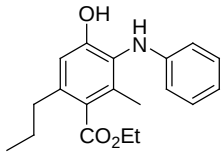
6-ethyl-4-Hydroxy-2-methyl-3-phenylamino-benzoic acid ethyl ester (106ja):



106ja

Purified by column chromatography using EtOAc/hexane and isolated as a solid. IR (neat): ν_{max} 3387 (O-*H* and N-*H*), 2974, 1701 (O-C=O), 1658, 1602 1498, 1176, 1051 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.17 (2H, t, *J* = 8.0 Hz), 6.83 (1H, t, *J* = 7.6 Hz), 6.78 (1H, s, O-*H*), 6.59 (2H, d, *J* = 8.0 Hz), 6.41 (1H, s), 4.91 (1H, s, N-*H*), 4.35 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 2.62 (2H, q, *J* = 8.0 Hz, C*H*$_2$CH$_3$), 2.07 (3H, s, Ar-C*H*$_3$), 1.36 (3H, t, *J* = 6.8 Hz, OCH$_2$C*H*$_3$), 1.24 (3H, t, *J* = 7.6 Hz, CH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 169.8 (C, O-C=O), 154.9 (C), 145.9 (C), 141.8 (C), 134.5 (C), 129.5 (2 x CH), 126.8 (C), 123.8 (C), 119.8 (CH), 114.1 (2 x CH), 112.5 (CH), 61.0 (CH_2, O*C*H_2CH$_3$), 26.8 (CH_2, C*H*$_2$CH$_3$), 15.4 (CH_3, Ar-*C*H_3), 15.2 (CH_3, OCH$_2$C*H*$_3$), 14.3 (CH_3, CH$_2$C*H*$_3$); LRMS m/z 298.15 (M – H^+), calcd $C_{18}H_{21}NO_3$ 299.1521; HRMS m/z 300.1592 (M + H^+), calcd $C_{18}H_{21}NO_3H^+$ 300.1599.

4-Hydroxy-2-methyl-3-phenylamino-6-propyl-benzoic acid ethyl ester (106ka):

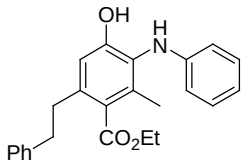


106ka

Purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 58 °C; IR (neat): ν_{max} 3371 (O-*H* and N-*H)*, 3051, 2961, 1720 (O-C=O), 1660, 1602, 1498, 1176, 1053, 748, 694 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.17 (2H, t, *J* = 8.0 Hz), 6.82 (1H, t, *J* = 7.6 Hz), 6.76 (1H, s), 6.58 (2H, d, *J* = 8.0 Hz), 6.39 (1H, s, O-*H*), 4.88 (1H, s, N-*H*), 4.34 (2H, q, *J* = 7.6 Hz, OC*H*$_2$CH$_3$), 2.56 (2H, t, *J* = 8.0 Hz, ArC*H*$_2$CH$_2$CH$_3$), 2.08 (3H, s, Ar-C*H*$_3$), 1.64 (2H, m, ArCH$_2$C*H*$_2$CH$_3$), 1.36 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$), 0.96 (3H, t, *J* = 8.0 Hz, ArCH$_2$CH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 169.7 (C, O-C=O), 154.7 (C), 145.8 (C), 140.4 (C), 134.5 (C), 129.5 (2 x CH), 127.0 (C), 123.8 (C), 119.8 (CH), 114.1 (2 x CH), 113.2 (CH), 61.0 (CH_2, O*C*H_2CH$_3$), 35.9 (CH_2, ArC*H*$_2$CH$_2$CH$_3$), 24.3 (CH_2, ArCH$_2$C*H*$_2$CH$_3$), 15.2 (CH_3, Ar-*C*H_3), 14.2 (CH_3,

OCH_2CH_3), 14.0 (CH_3, $ArCH_2CH_2CH_3$); LRMS m/z 312.20 ($M - H^+$), calcd $C_{19}H_{23}NO_3$ 313.1678; HRMS m/z 314.1747 ($M + H^+$), calcd $C_{19}H_{23}NO_3H^+$ 314.1756.

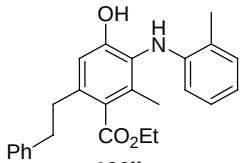
4-Hydroxy-2-methyl-6-phenethyl-3-phenylamino-benzoic acid ethyl ester (106la):



106la

Purified by column chromatography using EtOAc/hexane and isolated as orange oil. IR (neat): ν_{max} 3366 (O-*H* and N-*H*), 3026, 2986, 1699 (O-C=O), 1602, 1494, 1304, 1053, 750, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.29 (2H, t, *J* = 8.0 Hz), 7.18 (5H, m, Ph-*H)*, 6.82 (1H, t, *J* = 7.6 Hz), 6.76 (1H, s), 6.57 (2H, d, *J* = 8.0 Hz), 6.43 (1H, s, O-*H*), 4.93 (1H, s, N-*H*), 4.36 (2H, q, *J* = 6.8 Hz, OCH_2CH_3), 2.89 (4H, m, $PhCH_2CH_2Ar$), 2.08 (3H, s, Ar-CH_3), 1.35 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 169.7 (C, O-C=O), 154.8 (C), 145.8 (C), 141.5 (C), 139.5 (C), 134.8 (C), 129.5 (2 x CH), 128.4 (2 x CH), 128.3 (2 x CH), 126.9 (C), 126.0 (CH), 124.2 (C), 119.8 (CH), 114.0 (2 x CH), 113.3 (CH), 61.1 (CH_2, OCH_2CH_3), 37.6 (CH_2), 36.0 (CH_2), 15.2 (CH_3, Ar-CH_3), 14.2 (CH_3, OCH_2CH_3); LRMS m/z 374.15 ($M - H^+$), calcd $C_{24}H_{25}NO_3$ 375.1834; HRMS m/z 398.1731 ($M + Na^+$), calcd $C_{24}H_{25}NO_3Na$ 398.1732; Anal. calcd for $C_{24}H_{25}NO_3$ (375.18): C, 76.77; H, 6.71; N, 3.73. Found: C, 76.724; H, 6.733; N, 3.969%.

4-Hydroxy-2-methyl-6-phenethyl-3-o-tolylamino-benzoic acid ethyl ester (106lb):

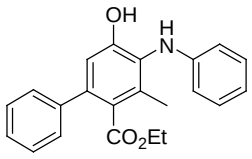


106lb

Purified by column chromatography using EtOAc/hexane and isolated as a light yellow solid. Mp 82 °C; IR (neat): ν_{max} 3383 (O-*H* and N-*H*), 3026, 2978, 1714 (O-C=O), 1587, 1498, 1365, 1111, 1051, 750, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.29 (2H, t, *J* = 7.6 Hz), 7.21 (3H, m), 7.13 (1H, d, *J* = 7.6 Hz), 7.00 (1H, t, *J* = 7.6 Hz), 6.78 (1H, s), 6.77 (1H, t, *J* = 8.0 Hz), 6.36 (1H, s, O-*H*), 6.25 (1H, d, *J* = 8.0 Hz), 4.75 (1H, s, N-*H*), 4.35 (2H, q, *J* = 6.8 Hz, OCH_2CH_3), 2.90 (4H, m, $PhCH_2CH_2Ar$), 2.34 (3H, s, Ar-CH_3), 2.06 (3H, s, Ar-CH_3), 1.35 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 169.6 (C, O-C=O), 154.6 (C), 143.6 (C), 141.5 (C), 139.4 (C), 134.4 (C), 130.5 (CH), 128.4 (2 x CH), 128.3 (2 x CH), 127.4 (CH), 127.0 (C), 126.0 (CH), 124.5

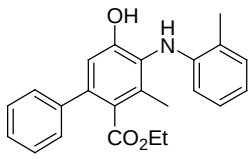
(C), 122.7 (C), 119.7 (CH), 113.4 (CH), 112.2 (CH), 61.1 (CH_2, O*C*H_2CH$_3$), 37.6 (CH_2), 36.0 (CH_2), 17.5 (CH_3, Ar-CH_3), 15.1 (CH_3, Ar-*C*H_3), 14.3 (CH_3, OCH$_2$C*H*$_3$); LRMS m/z 390.25 (M + H^+), calcd $C_{25}H_{27}NO_3$ 389.1991; HRMS m/z 412.1888 (M + Na), calcd $C_{25}H_{27}NO_3Na$ 412.1889; Anal. calcd for $C_{25}H_{27}NO_3$ (389.19): C, 77.09; H, 6.99; N, 3.60. Found: C, 77.245; H, 6.952; N, 3.891%.

5-Hydroxy-3-methyl-4-phenylamino-biphenyl-2-carboxylic acid ethyl ester (106ma): Purified by column chromatography using EtOAc/hexane and isolated as yellow solid. Mp 88 °C; IR (neat): ν_{max} 3371 (O-*H* and N-*H*), 2926, 1732 (O-C=O), 1668, 1602, 1498, 1157, 752, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.38 (5H, m, Ph-*H*), 7.22 (2H, t, *J* = 8.4 Hz), 6.93 (1H, s), 6.87 (1H, t, *J* = 7.2 Hz), 6.66 (2H, d, *J* = 8.0 Hz), 6.43 (1H, s, O-*H)*, 5.00 (1H, s, N-*H*), 3.98 (2H, q, *J* = 6.8 Hz, OC*H*$_2$CH$_3$), 2.20 (3H, s, Ar-C*H*$_3$), 0.90 (3H, t, *J* = 6.8 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 169.4 (C, O-C=O), 154.7 (C), 145.6 (C), 140.9 (C), 140.8 (C), 135.4(C), 129.6 (2 x CH), 128.2 (2 x CH), 128.1 (2 x CH), 127.4 (CH), 126.5 (C), 125.4 (C), 120.0 (CH), 114.2 (2 x CH), 113.9 (CH), 60.9 (CH_2, O*C*H_2CH$_3$), 15.2 (CH_3, Ar-*C*H_3), 13.5 (CH_3, OCH$_2$C*H*$_3$); LRMS m/z 346.05 (M – H^+), calcd $C_{22}H_{21}NO_3$ 347.1521; HRMS m/z 370.1415 (M + Na^+), calcd $C_{22}H_{21}NO_3Na^+$ 370.1419.



106ma

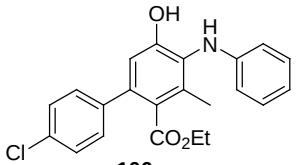
5-Hydroxy-3-methyl-4-o-tolylamino-biphenyl-2-carboxylic acid ethyl ester (106mb): Purified by column chromatography using EtOAc/hexane and isolated as a white solid. Mp 82 °C; IR (neat): ν_{max} 3385 (*O-H* and *N-H*), 3057, 2978, 1712 (O-C=O), 1587, 1498, 1471, 1111, 1051, 750, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.34 (5H, m, Ph-*H*), 7.17 (1H, d, *J* = 7.2 Hz), 7.05 (1H, t, *J*= 7.6 Hz), 6.95 (1H, s), 6.82 (1H, t, *J* = 7.2 Hz), 6.45 (1H, s, O-*H*), 6.35 (1H, d, *J* = 8.0 Hz), 4.83 (1H, s, N-*H*), 4.00 (2H, q, *J* = 7.6 Hz, OC*H*$_2$CH$_3$), 2.40 (3H, s, Ar-C*H*$_3$), 2.16 (3H, s, Ar-C*H*$_3$), 0.90 (3H, t, *J* = 7.6 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 169.4 (C, O-C=O), 154.5 (C), 143.4 (C), 140.9 (C), 140.8 (C), 135.0 (C), 130.6 (CH), 128.2 (2 x CH), 128.1 (2 x CH), 127.5 (CH), 127.4 (CH), 126.6 (C), 125.6 (C), 122.8 (C), 119.9 (CH), 113.9 (CH),



106mb

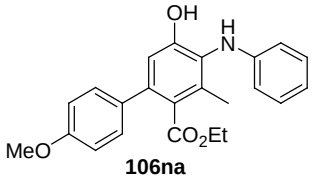
112.4 (CH), 60.9 (CH_2, O*C*H_2CH$_3$), 17.6 (CH_3, Ar-*C*H_3), 15.0 (CH_3, Ar-*C*H_3), 13.5 (CH_3, OCH$_2$C*H*$_3$); LRMS m/z 362.20 (M + H^+), calcd $C_{23}H_{23}NO_3$ 361.1678; HRMS m/z 384.1557 (M + Na), calcd $C_{23}H_{23}NO_3Na$ 384.1576; Anal. calcd for $C_{23}H_{23}NO_3$ (361.16): C, 76.43; H, 6.41; N, 3.88. Found: C, 76.539; H, 6.403; N, 3.985%.

4'-Chloro-5-hydroxy-3-methyl-4-phenylamino-biphenyl-2-carboxylic acid ethyl ester (106pa): Purified by column chromatography using EtOAc/hexane and isolated as yellow oil. IR (neat): ν_{max} 3389 (*O-H* and *N-H*), 2982, 1730 (O-C=O), 1670, 1597, 1493, 1199, 1091, 748, 694 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.39 (2H, d, *J* = 8.4 Hz), 7.34 (2H, d, *J* = 8.4 Hz), 7.25 (2H, t, *J* = 8.4 Hz), 6.92 (1H, s), 6.90 (1H, t, *J* = 7.2 Hz), 6.68 (2H, d, *J* = 8.4 Hz), 6.54 (1H, s, O-*H*), 5.00 (1H, s, N-*H*), 4.05 (2H, q, *J* = 6.8 Hz, OC*H*$_2$CH$_3$), 2.22 (3H, s, Ar-C*H*$_3$), 1.01 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 169.2 (C, O-C=O), 154.7 (C), 145.4 (C), 139.5 (C), 139.2 (C), 135.6 (C), 133.6 (C), 129.6 (2 x CH), 129.5 (2 x CH), 128.4 (2 x CH), 126.5 (C), 125.7 (C), 120.2 (CH), 114.3 (2 x CH), 113.8 (CH), 61.1 (CH_2, O*C*H_2CH$_3$), 15.2 (CH_3, Ar-*C*H_3), 13.7 (CH_3, OCH$_2$C*H*$_3$); LRMS m/z 380.10 (M – H^+), calcd $C_{22}H_{20}ClNO_3$ 381.1140; HRMS m/z 404.1014 (M + Na^+), calcd $C_{22}H_{20}ClNO_3Na^+$ 404.1029.



106pa

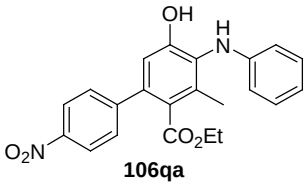
5-Hydroxy-4'-methoxy-3-methyl-4-phenylamino-biphenyl-2-carboxylic acid ethyl ester (106na): Purified by column chromatography using EtOAc/hexane and isolated as yellow liquid. IR (neat): ν_{max} 3385 (*O-H* and *N-H*), 2924, 1716 (O-C=O), 1604, 1502, 1406, 1248, 750, 694 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.31 (2H, d, *J* = 8.4 Hz), 7.21 (2H, d, *J* = 8.0 Hz), 6.93 (1H, s), 6.90 (2H, d, *J* = 7.6 Hz), 6.85 (1H, t, *J* = 7.2 Hz), 6.65 (2H, d, *J* = 8.4 Hz), 6.53 (1H, s, O-*H*), 5.00 (1H, s, N-*H*), 4.04 (2H, q, *J* = 6.8 Hz, OC*H*$_2$CH$_3$), 3.84 (3H, s, OC*H*$_3$), 2.17 (3H, s, Ar-C*H*$_3$), 0.99 (3H, t, *J* =6.8 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 169.7 (C, O-C=O), 159.1 (C), 154.6 (C), 145.7 (C), 140.3 (C), 135.2 (C), 133.1 (C), 129.6 (2 x CH), 129.2 (2 x CH), 126.6



106na

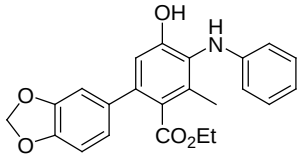
(C), 125.0 (C), 120.0 (CH), 114.2 (2 x CH), 113.8 (CH), 113.7 (2 x CH), 61.0 (CH_2, O*C*H_2CH$_3$), 55.3 (CH_3, OCH$_3$), 15.1 (CH_3, Ar-*C*H$_3$), 13.7 (CH_3, OCH$_2$C*H*$_3$); LRMS m/z 378.20 (M + H^+), calcd $C_{23}H_{23}NO_4$ 377.1627; HRMS m/z 378.1698 (M + H^+), calcd $C_{23}H_{23}NO_4H^+$ 378.1705.

5-Hydroxy-3-methyl-4'-nitro-4-phenylamino-biphenyl-2-carboxylic acid ethyl ester (106qa): Purified by column chromatography using EtOAc/hexane and isolated as a yellow solid. Mp 180 °C; IR (neat): ν_{max} 3404 (*O-H* and *N-H*), 2976, 1732 (O-C=O), 1684, 1593, 1516, 1055, 744, 692 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.27 (2H, d, *J* = 8.8 Hz), 7.55 (2H, d, *J* = 8.4 Hz), 7.24 (2H, t, *J* = 8.0 Hz), 6.92 (1H, s), 6.89 (1H, t, *J* = 7.2 Hz), 6.67 (2H, d, *J* = 8.0 Hz), 6.55 (1H, s, O-*H*), 5.00 (1H, s, N-*H*), 4.03 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 2.23 (3H, s, Ar-C*H*$_3$), 0.97 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 168.7 (C, O-C=O), 154.9 (C), 147.5 (C), 147.2 (C), 145.1 (C), 138.5 (C), 136.2 (C), 129.7 (2 x CH), 129.1 (2 x CH), 126.6 (C), 126.3 (C), 123.5 (2 x CH), 120.5 (CH), 114.5 (2 x CH), 113.8 (CH), 61.2 (CH_2, O*C*H_2CH$_3$), 15.3 (CH_3, Ar-*C*H$_3$), 13.7 (CH_3, OCH$_2$C*H*$_3$); LRMS m/z 391.10 (M – H^+), calcd $C_{22}H_{20}N_2O_5$ 392.1372; HRMS m/z 393.1467 (M H^+), calcd $C_{22}H_{20}N_2O_5H^+$ 393.1450.



106qa

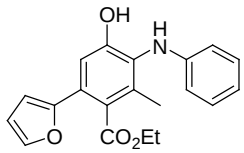
6-Benzo(1, 3)dioxol-5-yl-4-hydroxy-2-methyl-3-phenylamino-benzoic acid ethyl ester (**106oa**): Purified by column chromatography using EtOAc/hexane and isolated as yellow oil. IR (neat): ν_{max} 3371 (O-*H* and N-*H*), 3047, 2980, 1712 (O-C=O), 1602, 1500, 1039, 750, 694 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.22 (2H, t, *J* = 8.0 Hz), 6.91-6.83 (5H, m, Ar-*H)*, 6.67 (2H, d, *J* = 8.0 Hz), 6.00 (2H, s, OC*H*$_2$O), 5.06 (1H, s, N-*H*), 4.13 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 2.19 (3H, s, Ar-C*H*$_3$), 1.08 (3H, t, *J* = 7.6Hz, OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 169.5 (C, O-C=O), 154.5 (C), 147.5 (C), 147.0 (C), 145.7 (C), 140.2 (C), 135.2 (C), 134.7 (C), 129.6 (2 x CH), 126.6 (C), 125.3 (C), 121.7(CH), 119.9 (CH), 114.2 (2 x CH), 113.8 (CH), 108.8 (CH),



106oa

108.1 (CH), 101.1 (CH_2, O*C*H_2O), 61.0 (CH_2, O*CH*$_2$$CH_3$), 15.1 ($CH_3$, Ar-*C*$H_3$), 13.8 ($CH_3$, OCH_2C*H*$_3$); GCMS m/z 391 (M^+), calcd $C_{23}H_{21}NO_5$ (391.14); Anal. calcd for $C_{23}H_{21}NO_5$ (391.14): C, 70.58; H, 5.41; N, 3.58. Found: C, 70.644; H, 5.416; N, 3.924%.

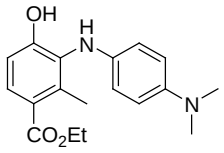
6-Furan-2-yl-4-hydroxy-2-methyl-3-phenylamino-benzoic acid ethyl ester (106ra):



106ra

Purified by column chromatography using EtOAc/hexane and isolated as a white solid. Mp 84 °C; IR (neat): ν_{max} 3383 (O-*H* and N-*H*), 2928, 1722 (O-C=O), 1602, 1498, 1367, 1199, 1055, 746, 694 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.46 (1H, d, *J* = 1.2 Hz), 7.20 (2H, t, *J* = 8.4 Hz), 7.17 (1H, s), 6.85 (1H, t, *J* = 7.6 Hz), 6.62 (2H, d, *J* = 8.0 Hz), 6.56 (1H, d, *J* = 3.0 Hz), 6.46 (1H, br d, *J* = 3.2 Hz*)*, 5.02 (1H, s, N-*H*), 4.30 (2H, q, *J* = 7.2 Hz, O*CH*$_2$$CH_3$), 2.14 (3H, s, Ar-C*H*$_3$), 1.25 (3H, t, *J* = 7.2 Hz, OCH_2C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 169.7 (C, O-C=O), 154.6 (C), 151.9 (C), 145.5 (C), 142.6 (CH), 135.1 (C), 129.6 (2 x CH), 128.2 (C), 125.8 (C), 124.4 (C), 120.1 (CH), 114.2 (2 x CH), 111.6 (CH), 110.7 (CH), 107.7 (CH), 61.4 (CH_2, O*CH*$_2$$CH_3$), 14.9 ($CH_3$, Ar-*C*$H_3$), 14.1 ($CH_3$, OCH_2C*H*$_3$); GCMS m/z 337 (M^+), calcd $C_{20}H_{19}NO_4$ (337.13); Anal. calcd for $C_{20}H_{19}NO_4$ (337.13): C, 71.20; H, 5.68; N, 4.15. Found: C, 71.187; H, 5.689; N, 4.199%.

3-(4-Dimethylamino-phenylamino)-4-hydroxy-2-methyl-benzoic acid ethyl ester (106ac):



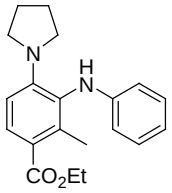
106ac

Purified by column chromatography using EtOAc/hexane and isolated as a dark greenish liquid. IR (neat): ν_{max} 3391 (O-*H* and N-*H)*, 2978, 1712 (O-C=O), 1589, 1516, 1053, 779 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.85 (1H, d, *J* = 8.4 Hz), 6.90 (1H, d, *J* = 8.8 Hz), 6.67 (2H, d, *J* = 6.8 Hz), 6.53 (2H, d, *J* = 8.8 Hz), 4.75 (1H, br s, N-*H*), 4.31 (2H, q, *J* = 7.2 Hz, O*CH*$_2$$CH_3$), 2.83 (6H, s, N(C*H*$_3$)$_2$), 2.41 (3H, s, Ar-C*H*$_3$), 1.34 (3H, t, *J* = 7.2 Hz, OCH_2C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.3 (C, O-C=O), 157.3 (C), 145.6 (C), 140.0 (C), 137.0 (C), 130.9 (CH), 128.0 (C), 122.8 (C), 115.6 (2 x CH), 115.1 (2 x CH), 111.6 (CH), 60.5 (CH_2, OCH_2*CH*$_3$), 41.7 (CH_3, N(*CH*$_3$)$_2$), 15.6 (CH_3, Ar-*C*H_3),

14.3 (CH_3, OCH_2CH_3); LRMS m/z 314.1 (M^+), calcd $C_{18}H_{22}N_2O_3$ (314.16); Anal. calcd for $C_{18}H_{22}N_2O_3$ (314.16): C, 68.77; H, 7.05; N, 8.91. Found: C, 68.825; H, 7.043; N, 9.142%.

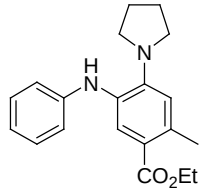
4b: Self-catalyzed three-component cascade enamine amination/iso-aromatization reactions: In an ordinary glass vial equipped with a magnetic stirring bar, to 0.3 mmol of the pyrrolidine, 0.6 mmol of Hagemann's esters **88** and 300 mg of MS 4A° was added 0.5 mL of solvent, and then the 0.5 mL solution of nitrosobenzene (0.3 mmol) **56** was added dropwise for 0.5 h and the reaction mixture was stirred at 25 °C for the time indicated in Tables 12 and 14. The crude reaction mixture was worked up with aqueous NH_4Cl solution and the aqueous layer was extracted with dichloromethane (2 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure cascade products **107** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

2-Methyl-3-phenylamino-4-pyrrolidin-1-yl-benzoic acid ethyl ester (107aa):



107aa

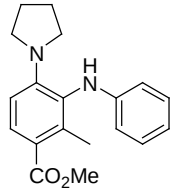
Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 76 °C; IR (neat): ν_{max} 3381 (N-*H*), 2970, 1705 (O-C=O), 1597, 1498, 1167, 1055, 748, 694 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.81 (1H, d, *J* = 8.8 Hz), 7.17 (2H, t, *J* = 8.0 Hz), 6.75 (1H, t, *J* = 7.2 Hz), 6.69 (1H, d, *J* = 8.8 Hz), 6.50 (2H, d, *J* = 8.4 Hz), 5.18 (1H, s, N-*H*), 4.33 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 3.30 (4H, t, *J* = 6.4 Hz), 2.44 (3H, s, Ar-C*H*$_3$), 1.82 (4H, m), 1.39 (3H, t, *J* = 6.8 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.8 (C, O-C=O), 150.4 (C), 146.5 (C), 140.4 (C), 129.4 (CH), 129.0 (2 x CH), 127.1 (C), 120.2 (C), 117.7 (CH), 113.1 (2 x CH), 111.9 (CH), 60.1 (CH_2, O*C*H$_2$CH$_3$), 50.6 (2 x CH_2), 25.4 (2 x CH_2), 16.0 (CH_3, Ar-*C*H$_3$), 14.3 (CH_3, OCH$_2$C*H*$_3$); LRMS m/z 325.25 ($M + H^+$), calcd $C_{20}H_{24}N_2O_2$ 324.1838; HRMS m/z 325.1902 ($M + H^+$), calcd $C_{20}H_{24}N_2O_2H^+$ 325.1916; Anal. calcd for $C_{20}H_{24}N_2O_2$ (324.18): C, 74.04; H, 7.46; N, 8.64. Found: C, 74.038; H, 7.465; N, 8.508%.



108aa

2-Methyl-5-phenylamino-4-pyrrolidin-1-yl-benzoic acid ethyl ester (108aa): Purified by column chromatography using EtOAc/hexane and isolated as liquid. IR (neat): ν_{max} 3379 (N-*H)*, 2966, 1707 (O-C=O), 1599, 1498, 1076, 748, 694 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.81 (1H, s), 7.19 (2H, t, *J* = 7.2 Hz), 6.78 (1H, t, *J* = 7.2 Hz), 6.70 (2H, d, *J* = 7.6 Hz), 6.61 (1H, s), 5.28 (1H, s, N-*H*), 4.26 (2H, q, *J* = 7.2 Hz, OCH_2CH_3), 3.32 (4H, t, *J* = 6.4 Hz), 2.58 (3H, s, Ar-CH_3), 1.84 (4H, m), 1.32 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.1 (C, O-C=O), 148.0 (C), 146.3 (C), 138.2 (C), 129.3 (CH), 129.2 (2 x CH), 126.9 (C), 119.2 (C), 118.5 (CH), 118.3 (CH), 114.4 (2 x CH), 60.0 (CH_2, OCH_2CH_3), 50.1 (2 x CH_2), 25.2 (2 x CH_2), 22.0 (CH_3, Ar-CH_3), 14.4 (CH_3, OCH_2CH_3); LRMS m/z 325.30 ($M + H^+$), calcd $C_{20}H_{24}N_2O_2$ 324.1838.

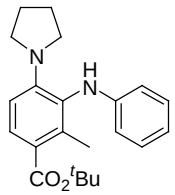
2-Methyl-3-phenylamino-4-pyrrolidin-1-yl-benzoic acid methyl ester (107sa):



107sa

Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 96 °C; IR (neat): ν_{max} 3395 (N-*H)*, 2932, 1701 (O-C=O), 1602, 1508, 1055, 746, 694 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.79 (1H, d, *J* = 8.8 Hz), 7.17 (2H, t, *J* = 7.6 Hz), 6.74 (1H, t, *J* = 7.2 Hz), 6.68 (1H, d, *J* = 8.8 Hz), 6.50 (2H, d, *J* = 8.0 Hz), 5.17 (1H, s, N-*H*), 3.85 (3H, s, OCH_3), 3.31 (4H, t, *J* = 6.4 Hz), 2.43 (3H, s, Ar-CH_3), 1.83 (4H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 168.2 (C, O-C=O), 150.6 (C), 146.6 (C), 140.8 (C), 129.6 (CH), 129.3 (2 x CH), 127.2 (C), 119.9 (C), 117.9 (CH), 113.2 (2 x CH), 112.0 (CH), 51.5 (CH_3, OCH_3), 50.7 (2 x CH_2), 25.6 (2 x CH_2), 14.2 (CH_3, Ar-CH_3); LRMS m/z 311.20 ($M + H^+$), calcd $C_{19}H_{22}N_2O_2$ 310.1839; HRMS m/z 311.1744 ($M + H^+$), calcd $C_{19}H_{22}N_2O_2H^+$ 311.1759.

2-Methyl-3-phenylamino-4-pyrrolidin-1-yl-benzoic acid tert-butyl ester (107ba):

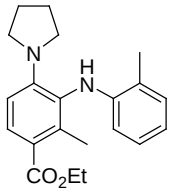


107ba

Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 110 °C; IR (neat): ν_{max} 3385 (N-*H)*, 2966, 1703 (O-C=O), 1599, 1498, 1415, 1149, 1080, 746, 692 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.67 (1H, d, *J* = 8.8 Hz), 7.16 (2H, t, *J* = 8.0 Hz), 6.72 (1H, t, *J* = 7.2

Hz), 6.66 (1H, d, *J* = 8.8 Hz), 6.48 (2H, d, *J* = 8.0 Hz), 5.15 (1H, s, N-*H*), 3.23 (4H, t, *J* = 6.4 Hz), 2.38 (3H, s, Ar-C*H*$_3$), 1.78 (4H, p, *J* = 6.4 Hz), 1.24 (9H, s, 3 x CH_3, OC(C*H*$_3$)$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.4 (C, O-C=O), 150.0 (C), 146.5 (C), 139.5 (C), 129.1 (CH), 129.0 (2 x CH), 127.5 (C), 122.5 (C), 117.8 (CH), 113.2 (2 x CH), 112.0 (CH), 80.1 (C, O*C*(CH$_3$)$_3$), 50.6 (2 x CH_2), 28.3 (3 x CH_3, OC(*C*H$_3$)$_3$), 25.4 (2 x CH_2), 16.1 (CH_3, Ar-*C*H$_3$); LRMS m/z 353.30 (M + H^+), calcd $C_{22}H_{28}N_2O_2$ 352.2151; HRMS m/z 353.2216 (M + H^+), calcd $C_{22}H_{28}N_2O_2H^+$ 353.2229; Anal. calcd for $C_{22}H_{28}N_2O_2$ (352.21): C, 74.97; H, 8.01; N, 7.95. Found: C, 74.782; H, 8.049; N, 8.010%.

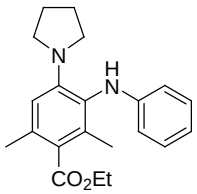
2-Methyl-4-pyrrolidin-1-yl-3-o-tolyl amino-benzoic acid ethyl ester (107ab):



107ab

Purified by column chromatography using EtOAc/hexane and isolated as a light yellow solid. Mp 88 °C; IR (neat): ν_{max} 3048 (N-H), 2968, 1703 (O-C=O), 1587, 1500, 1257, 1053, 748 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.77 (1H, d, *J* = 8.8 Hz), 7.12 (1H, d, *J* = 7.2 Hz), 7.00 (1H, t, *J* = 8.0 Hz), 6.75 (2H, m), 6.21 (1H, d, *J* = 7.6 Hz), 5.00 (1H, s, N-*H*), 4.30 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 3.28 (4H, t, *J* = 6.8 Hz), 2.35 (3H, s, Ar-C*H*$_3$), 2.30 (3H, s, Ar-C*H*$_3$), 1.80 (4H, m), 1.37 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.9 (C, O-C=O), 150.2 (C), 144.5 (C), 139.8 (C), 130.1 (CH), 129.2 (CH), 127.9 (C), 126.9 (CH), 121.7 (C), 120.8 (C), 117.8 (CH), 112.2 (CH), 111.9 (CH), 60.2 (CH_2, O*C*H$_2$CH$_3$), 50.4 (2 x CH_2), 25.4 (2 x CH_2), 17.7 (CH_3, Ar-*C*H$_3$), 16.0 (CH_3, Ar-*C*H$_3$), 14.4 (CH_3, OCH$_2$C*H*$_3$); LRMS m/z 339.30 (M + H^+), calcd $C_{21}H_{26}N_2O_2$ 338.1994; HRMS m/z 361.1892 (M + Na^+), calcd $C_{21}H_{26}N_2O_2Na$ 361.1892.

2,6-Dimethyl-3-phenylamino-4-pyrrolidin-1-yl-benzoic acid ethyl ester (107ia):

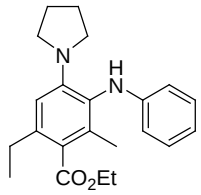


107ia

Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 90 °C; IR (neat): ν_{max} 3383 (N-*H)*, 2970, 1705 (O-C=O), 1601, 1500, 1101, 1053, 748, 694 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.16 (2H, t, *J* = 7.6 Hz), 6.74 (1H, t, *J* = 7.2 Hz), 6.57 (1H, s), 6.53 (2H, d, *J* = 7.6 Hz), 5.17 (1H, s, N-*H*), 4.37 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 3.18 (4H, t, *J* = 6.8 Hz), 2.34 (3H, s, Ar-C*H*$_3$), 2.13 (3H, s, Ar-C*H*$_3$), 1.80

(4H, m), 1.38 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 170.2 (C, O-C=O), 148.0 (C), 146.5 (C), 134.6 (C), 133.0 (C), 129.0 (2 x CH), 126.0 (C), 125.6 (C), 117.8 (CH), 115.1 (CH), 113.4 (2 x CH), 60.6 (CH_2, OCH_2CH_3), 50.7 (2 x CH_2), 25.3 (2 x CH_2), 20.2 (CH_3, Ar-CH_3), 15.9 (CH_3, Ar-CH_3), 14.3 (CH_3, OCH_2CH_3); LRMS m/z 339.20 ($M + H^+$), calcd $C_{21}H_{26}N_2O_2$ 338.1994; HRMS m/z 339.2085 ($M + H^+$), calcd $C_{21}H_{26}N_2O_2H^+$ 339.2073; Anal. calcd for $C_{21}H_{26}N_2O_2$ (338.19): C, 74.52; H, 7.74; N, 8.28. Found: C, 74.551; H, 7.745; N, 8.255%.

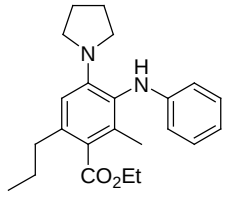
6-Ethyl-2-methyl-3-phenylamino-4-pyrrolidin-1-yl-benzoic acid ethyl ester (107ja):



107ja

Purified by column chromatography using EtOAc/hexane and isolated as a solid. IR (neat): ν_{max} 3389 (N-*H*), 2968, 1714 (O-C=O), 1599, 1516, 1107, 1053, 748, 694 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.16 (2H, t, *J* = 7.6 Hz), 6.74 (1H, t, *J* = 7.2 Hz), 6.61 (1H, s), 6.54 (2H, d, *J* = 7.6 Hz), 5.18 (1H, s, N-*H*), 4.37 (2H, q, *J* = 7.2 Hz, OCH_2CH_3), 3.12 (4H, t, *J* = 6.8 Hz), 2.64 (2H, q, *J* = 7.2 Hz, $ArCH_2CH_3$), 2.12 (3H, s, Ar-CH_3), 1.80 (4H, m), 1.38 (3H, t, *J* = 7.2 Hz, OCH_2CH_3), 1.26 (3H, t, *J* = 7.2 Hz, $ArCH_2CH_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 170.3 (C, O-C=O), 148.1 (C), 146.5 (C), 139.1 (C), 134.2 (C), 129.0 (2 x CH), 126.3 (C), 125.4 (C), 117.8 (CH), 113.7 (CH), 113.5 (2 x CH), 60.7 (CH_2, OCH_2CH_3), 50.7 (2 x CH_2), 27.2 (CH_2, $ArCH_2CH_3$), 25.2 (2 x CH_2), 15.9 (CH_3, Ar-CH_3), 15.8 (CH_3, OCH_2CH_3), 14.2 (CH_3, $ArCH_2CH_3$); LRMS m/z 353.25 ($M + H^+$), calcd $C_{22}H_{28}N_2O_2$ 352.2151; HRMS m/z 375.2042 ($M + Na^+$), calcd $C_{22}H_{28}N_2O_2Na^+$ 375.2048.

2-Methyl-3-phenylamino-6-propyl-4-pyrrolidin-1-yl-benzoic acid ethyl ester (107ka):

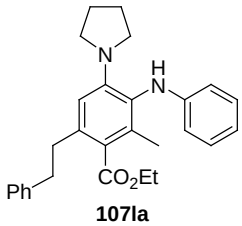


107ka

Purified by column chromatography using EtOAc/hexane and isolated as a solid. IR (neat): ν_{max} 3381 (N-*H*), 2957, 1720 (O-C=O), 1604, 1504, 1228, 1049, 746, 692 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.16 (2H, t, *J* = 8.4 Hz), 6.74 (1H, t, *J* = 7.2 Hz), 6.59 (1H, s), 6.54 (2H, d, *J* = 8.4 Hz), 5.18 (1H, s, N-*H*), 4.36 (2H, q, *J* = 7.2 Hz, OCH_2CH_3), 3.18 (4H, t, *J* = 6.4 Hz), 2.58 (2H, t, *J* = 8.0 Hz, $ArCH_2CH_2CH_3$), 2.12 (3H, s, Ar-CH_3), 1.80 (4H, m), 1.66 (2H, m, $ArCH_2CH_2CH_3$), 1.38 (3H, t, *J* = 7.2 Hz,

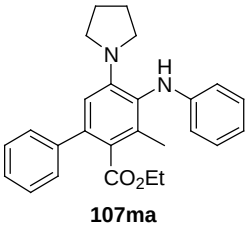
OCH_2CH_3), 0.99 (3H, t, *J* = 7.2 Hz, $ArCH_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 170.3 (C, O-C=O), 147.9 (C), 146.5 (C), 137.6 (C), 134.2 (C), 129.0 (2 x CH), 126.3 (C), 125.6 (C), 117.8 (CH), 114.4 (CH), 113.5 (2 x CH), 60.6 (CH_2, OCH_2CH_3), 50.7 (2 x CH_2), 36.3 (CH_2, $ArCH_2CH_2CH_3$), 25.2 (2 x CH_2), 24.7 (CH_2, $ArCH_2CH_2CH_3$), 15.9 (CH_3, Ar-CH_3), 14.3 (CH_3, OCH_2CH_3), 14.2 (CH_3, $ArCH_2CH_2CH_3$); LRMS m/z 367.35 ($M + H^+$), calcd $C_{23}H_{30}N_2O_2$ 366.2307; HRMS m/z 389.2200 ($M + Na^+$), calcd $C_{23}H_{30}N_2O_2Na^+$ 389.2205.

2-Methyl-6-phenethyl-3-phenylamino-4-pyrrolidin-1-yl-benzoic acid ethyl ester (107la): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 54 °C; IR (neat): ν_{max} 3389 (N-*H*), 2964, 1716 (O-C=O), 1602, 1498, 1053, 748, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.32 (2H, t, *J* = 7.6 Hz), 7.23 (5H, m, Ph-*H)*, 6.76 (1H, t, *J* = 7.2 Hz), 6.56 (2H, d, *J* = 8.4 Hz), 6.52 (1H, s), 5.20 (1H, s, N-*H*), 4.40 (2H, q, *J* = 6.8 Hz, OCH_2CH_3), 3.15 (4H, t, *J* = 6.4 Hz), 2.94 (4H, m), 2.16 (3H, s, Ar-CH_3), 1.80 (4H, m), 1.40 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 170.2 (C, O-C=O), 147.9 (C), 146.4 (C), 141.9 (C), 136.6 (C), 134.4 (C), 129.0 (2 x CH), 128.4 (2 x CH), 128.3 (2 x CH), 126.6 (C), 125.8 (CH), 125.5 (C), 117.9 (CH), 114.7 (CH), 113.5 (2 x CH), 60.8 (CH_2, OCH_2CH_3), 50.7 (2 x CH_2), 38.1 (CH_2), 36.4 (CH_2), 25.2 (2 x CH_2), 16.0 (CH_3, Ar-CH_3), 14.3 (CH_3, OCH_2CH_3); LRMS m/z 427.05 ($M - H^+$), calcd $C_{28}H_{32}N_2O_2$ 428.2464; HRMS m/z 429.2538 (M + H^+), calcd $C_{28}H_{32}N_2O_2H^+$ 429.2542.



107la

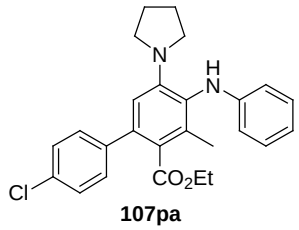
3-Methyl-4-phenylamino-5-pyrrolidin-1-yl-biphenyl-2-carboxylic acid ethyl ester (107ma): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 118 °C; IR (neat): ν_{max} 3335 (N-*H*), 2970, 1705 (O-C=O), 1601, 1498, 1053, 748, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38 (5H, m, Ph-*H)*, 7.21 (2H, t, *J* = 8.0 Hz), 6.78 (1H, t, *J* = 7.2 Hz), 6.74 (1H, s), 6.62 (2H, d, *J* = 8.4 Hz), 5.31 (1H, s, N-*H*), 4.01 (2H, q, *J* = 7.2 Hz, OCH_2CH_3), 3.22 (4H, t, *J* = 6.4 Hz), 2.22 (3H, s, Ar-CH_3), 1.81 (4H, m), 0.92 (3H, t, *J* = 6.8 Hz, OCH_2CH_3); ^{13}C NMR



107ma

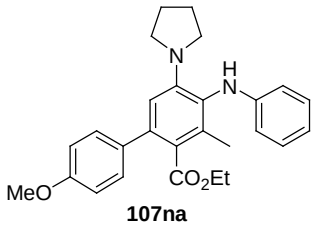
($CDCl_3$, DEPT-135) δ 170.0 (C, O-C=O), 147.8 (C), 146.2 (C), 141.9 (C), 138.3 (C), 134.9 (C), 129.1 (2 x CH), 128.2 (2 x CH), 128.0 (2 x CH), 127.7 (C), 127.0 (CH), 125.1 (C), 118.1 (CH), 115.0 (CH), 113.7 (2 x CH), 60.6 (CH_2, O*C*$H_2$$CH_3$), 50.8 (2 x CH_2), 25.2 (2 x CH_2), 15.9 (CH_3, Ar-*C*H_3), 13.6 (CH_3, OCH_2C*H*$_3$); LRMS m/z 401.30 (M + H^+), calcd $C_{26}H_{28}N_2O_2$ 400.2151; HRMS m/z 401.2216 (M + H^+), calcd $C_{26}H_{28}N_2O_2H^+$ 401.2229.

4'-Chloro-3-methyl-4-phenylamino-5-pyrrolidin-1-yl-biphenyl-2-carboxylic acid ethyl ester (107pa): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 104 °C; IR (neat): ν_{max} 3369 (*N-H*), 1718 (O-C=O), 1601, 1496, 748, cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.36 (4H, m, Ar-H), 7.20 (2H, t, *J* = 7.6 Hz), 6.78 (1H, t, *J* = 7.6 Hz), 6.68 (1H, s), 6.60 (2H, d, *J* = 8.4 Hz), 5.30 (1H, s, N-*H*), 4.04 (2H, q, *J* = 7.2 Hz, OC*H*$_2$$CH_3$), 3.22 (4H, t, *J* = 6.4 Hz), 2.20 (3H, s, Ar-C*H*$_3$), 1.82 (4H, m), 0.99 (3H, t, *J* = 7.2 Hz, OCH_2C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 169.8 (C, O-C=O), 147.9 (C), 146.1 (C), 140.3 (C), 136.9 (C), 135.1(C), 133.0 (C), 129.5 (2 x CH), 129.1 (2 x CH), 128.2 (2 x CH), 127.9 (C), 124.9 (C), 118.2 (CH), 114.8 (CH), 113.7 (2 x CH), 60.7 (CH_2, O*C*$H_2$$CH_3$), 50.8 (2 x CH_2), 25.3 (2 x CH_2), 15.9 (CH_3, Ar-*C*H_3), 13.7 (CH_3, OCH_2C*H*$_3$); LRMS m/z 433.00 (M – H^+), calcd $C_{26}H_{27}ClN_2O_2$ 434.1761; HRMS m/z 435.1821 (M + H^+), calcd $C_{26}H_{27}ClN_2O_2H^+$ 435.1839.



107pa

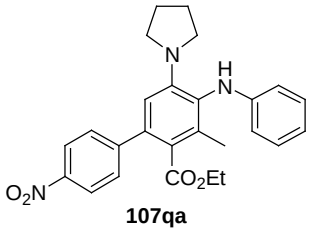
4'-Methoxy-3-methyl-4-phenylamino-5-pyrrolidin-1-yl-biphenyl-2-carboxylic acid ethyl ester (107na): Purified by column chromatography using EtOAc/hexane and isolated as yellow oil. IR (neat): ν_{max} 3383 (*N-H*), 2964, 1714 (O-C=O), 1602, 1500, 1141, 1053, 748, 694 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.33 (2H, d, *J* = 8.4 Hz), 7.19 (2H, t, *J* = 8.0 Hz), 6.92 (2H, d, *J* = 8.4 Hz), 6.76 (1H, t, *J* = 7.6 Hz), 6.70 (1H, s), 6.61 (2H, d, *J* = 7.6 Hz), 5.27 (1H, s, N-*H*), 4.04 (2H, q, *J* = 6.8 Hz, OC*H*$_2$$CH_3$), 3.84 (3H, s, OC*H*$_3$), 3.19 (4H, t, *J* = 6.4 Hz), 2.18 (3H, s, Ar-C*H*$_3$), 1.80



107na

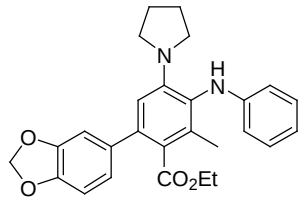
(4H, m), 0.98 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 170.2 (C, O-C=O), 158.8 (C), 147.8 (C), 146.3 (C), 137.7 (C), 134.6 (C), 134.3 (C), 129.3 (2 x CH), 129.1 (2 x CH), 127.6 (C), 125.4 (C), 118.1 (CH), 115.1 (CH), 113.7 (2 x CH), 113.5 (2 x CH), 60.6 (CH_2, OCH_2CH_3), 55.3 (CH_3, OCH_3), 50.8 (2 x CH_2), 25.3 (2 x CH_2), 15.9 (CH_3, Ar-CH_3), 13.8 (CH_3, OCH_2CH_3); LRMS m/z 427.25 (M□– 3), calcd $C_{27}H_{30}N_2O_3$ 430.2256; HRMS m/z 431.2325 (M +□ H^+), calcd $C_{27}H_{30}N_2O_3H^+$ 431.2334; Anal. calcd for $C_{27}H_{30}N_2O_3$ (430.22): C, 75.32; H, 7.02; N, 6.51. Found: C, 75.376; H, 7.006; N, 6.548%.

3-methyl-4'-nitro-4-phenylamino-5-pyrrolidin-1-yl-biphenyl-2-carboxylic acid ethyl ester (107qa): Purified by column chromatography using EtOAc/hexane and isolated as a yellow liquid. IR (neat): ν_{max} 3387 (*N-H*), 2966, 1716 (O-C=O), 1602, 1500, 1105, 1080, 748, 694 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.25 (2H, d, *J* = 8.8 Hz), 7.56 (2H, d, *J* = 8.4 Hz), 7.20 (2H, t, *J* = 8.0 Hz), 6.79 (1H, t, *J* = 8.4 Hz), 6.66 (1H, s), 6.61 (2H, d, *J* = 8.0 Hz), 5.32 (1H, s, N-*H*), 4.02 (2H, q, *J* = 7.2 Hz, OCH_2CH_3), 3.23 (4H, m), 2.21 (3H, s, Ar-CH_3), 1.82 (4H, m), 0.97 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 169.4 (C, O-C=O), 148.9 (C), 148.0 (C), 146.8 (C), 145.8 (C), 136.0 (C), 135.6 (C), 129.1 (2 x CH), 129.0 (2 x CH), 128.6 (C), 124.6 (C), 123.4 (2 x CH), 118.5 (CH), 114.5 (CH), 113.8 (2 x CH), 60.9 (CH_2, OCH_2CH_3), 50.8 (2 x CH_2), 25.3 (2 x CH_2), 16.0 (CH_3, Ar-CH_3), 13.7 (CH_3, OCH_2CH_3); LRMS m/z 446.20 (M + H^+), calcd $C_{26}H_{27}N_3O_4$ 445.2002; HRMS m/z 446.2085 (M + H^+), calcd $C_{26}H_{27}N_3O_4H^+$ 446.2080; Anal. calcd for $C_{26}H_{27}N_3O_4$ (445.20): C, 70.09; H, 6.11; N, 9.43. Found: C, 70.036; H, 6.134; N, 9.381%.



107qa

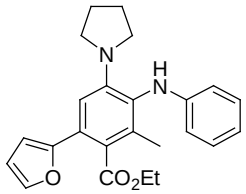
6-Benzo[1,3]dioxol-5-yl-2-methyl-3-phenylamino-4-pyrrolidin-1-yl-benzoic acid ethyl ester (107oa): Purified by column chromatography using EtOAc/hexane and isolated as a solid. IR (neat): ν_{max}



107oa

3362 (*N-H*), 2964, 1712 (O-C=O), 1601, 1577, 1502, 748 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.21 (2H, t, *J* = 8.0 Hz), 6.94 (1H, d, *J* = 1.6 Hz), 6.90-6.81 (2H, m), 6.79 (1H, t, *J* = 8.0 Hz), 6.71 (1H, br s), 6.62 (2H, d, *J* = 8.0 Hz), 6.00 (2H, s, OCH_2O), 5.29 (1H, s, N-*H*), 4.11 (2H, q, *J* = 7.2 Hz, OCH_2CH_3), 3.21 (4H, m), 2.20 (3H, s, Ar-CH_3), 1.83 (4H, m), 1.08 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 170.1 (C, O-C=O), 147.8 (C), 147.4 (C), 146.8 (C), 146.2 (C), 137.7 (C), 135.8 (C), 134.7 (C), 129.1 (2 x CH), 127.7 (C), 125.4 (C), 121.7 (CH), 118.2 (CH), 115.0 (CH), 113.8 (2 x CH), 109.0 (CH), 108.1 (CH), 101.0 (CH_2, OCH_2O), 60.7 (CH_2, OCH_2CH_3), 50.9 (2 x CH_2), 25.3 (2 x CH_2), 15.9 (CH_3, Ar-CH_3), 13.9 (CH_3, OCH_2CH_3); GCMS m/z 443.95 (M), calcd $C_{27}H_{28}N_2O_4$ 444.21; Anal. calcd for $C_{27}H_{28}N_2O_4$ (444.2049): C, 72.95; H, 6.35; N, 6.30; O, 14.40. Found: C, 72.996; H, 6.398; N, 6.382%.

6-Furan-2-yl-2-methyl-3-phenylamino-4-pyrrolidin-1-yl-benzoic acid ethyl ester (107ra): Purified by column chromatography using EtOAc/hexane and isolated as a solid. IR (neat): ν_{max} 3383 (*N-H*), 3051, 2972, 1716 (O-C=O), 1602, 1500, 1053, 736, 696 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.45 (1H, br s), 7.17 (2H, t, *J* = 7.2 Hz), 7.02 (1H, s), 6.77 (1H, t, *J* = 7.2 Hz), 6.58 (2H, d, *J* = 7.6 Hz), 6.50 (1H, d, *J* = 3.2 Hz), 6.44 (1H, m), 5.33 (1H, s, N-*H*), 4.29 (2H, q, *J* = 7.2 Hz, OCH_2CH_3), 3.18 (4H, m), 2.14 (3H, s, Ar-CH_3), 1.81 (4H, m), 1.25 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 170.3 (C, O-C=O), 153.0 (C), 147.7 (C), 146.0 (C), 142.1 (CH), 134.1 (C), 129.1 (2 x CH), 129.0 (C), 125.8 (C), 123.9 (C), 118.5 (CH), 114.0 (2 x CH), 112.4 (CH), 111.5 (CH), 106.8 (CH), 61.1 (CH_2, OCH_2CH_3), 50.9 (2 x CH_2), 25.2 (2 x CH_2), 15.7 (CH_3, Ar-CH_3), 14.1 (CH_3, OCH_2CH_3); GCMS m/z 389.95 (M), calcd $C_{24}H_{26}N_2O_3$ 390.19; Anal. calcd for $C_{24}H_{26}N_2O_3$ (390.1943): C, 73.82; H, 6.71; N, 7.17; O, 12.29. Found: C, 73.715; H, 6.762; N, 7.041%.



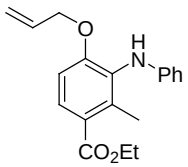
107ra

4c: Piperidine-catalyzed combination of cascade Knoevenagel/Michael/aldol condenasation/decarboxylation and cascade enamine amination/iso-aromatization

reactions in one-pot: To a stirred solution of ethyl acetoacetate (0.6 mmol) and aldehydes (0.3 mmol) in EtOH (1 mL) was added a catalytic amount of piperidine (0.1 mmol, 35 mol%) and the reaction mixture was stirred at 80 °C for 3 h. Solvent ethanol and piperidine was evaporated by vacuum pump; then catalyst piperidine (0.06 mmol, 20 mol%), nitrosobenzene **56a** (0.3 mmol) and solvent DMSO (1 mL) was added and the reaction mixture was stirred at 25 °C for 1-2 h. The crude reaction mixture was worked up with aqueous NH_4Cl solution and the aqueous layer was extracted with dichloromethane (2 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure one-pot products **106** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

4d: Pyrrolidine/Cs_2CO_3-catalyzed three-component enamine amination/iso-aromatization/alkylation reactions in one-pot: In an ordinary glass vial equipped with a magnetic stirring bar, to 0.6 mmol of the Hagemann's esters **88** was added 1.0 mL of solvent, and then the catalyst pyrrolidine (0.015 mmol, 2.5 μL) was added and the reaction mixture was stirred at 25 °C for the 0.5 h; then 0.3 mmol of nitrosobenzene **56a** was added in one-portion and the reaction mixture was stirred at 25 °C for the time indicated in Table 16. To the reaction mixture, alkyl halide (0.39 mmol) and Cs_2CO_3 (0.45 mmol) was added and stirring continued at RT for 24 h. The crude reaction mixture was worked up with aqueous NH_4Cl solution and the aqueous layer was extracted with dichloromethane (2 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure one-pot products **109** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

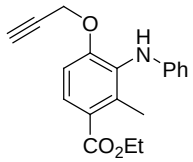
4-Allyloxy-2-methyl-3-phenylamino-benzoic acid ethyl ester (109aa): Purified by column chromatography using EtOAc/hexane and isolated as a light yellow liquid. IR (neat): ν_{max} 3387 (N-*H)*, 2928, 1709 (O-C=O), 1601, 1498, 1267, 1055, 748, 694 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.77 (1H, d, *J* = 8.8 Hz), 7.18 (2H, t, *J* = 8.4 Hz), 6.82 (1H, d, *J* = 8.8 Hz), 6.81 (1H, t, *J* = 8.8 Hz), 6.62 (2H, d, *J* = 7.6 Hz), 5.95 (1H, m, olefinic-*H*), 5.72 (1H, s,



109aa

N-*H*), 5.28 (1H, dd, *J* = 17.6 Hz, 4.0 Hz), 5.23 (1H, dd, *J* = 17.6 Hz, 4.0 Hz), 4.56 (2H, m), 4.36 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 2.42 (3H, s, Ar-C*H*$_3$), 1.39 (3H, t, *J* = 6.8 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 167.6 (C, O-C=O), 155.5 (C), 145.9 (C), 137.5 (C), 132.5 (CH), 130.6 (C), 129.0 (2 x CH), 128.0 (CH), 123.9 (C), 119.4 (CH), 117.8 (CH$_2$, CH=*C*H$_2$), 115.2 (2 x CH), 108.9 (CH), 69.1 (CH$_2$, O*C*H$_2$CH=CH$_2$), 60.6 (CH$_2$, O*C*H$_2$CH$_3$), 16.5 (CH$_3$, Ar-*C*H$_3$), 14.4 (CH$_3$, OCH$_2$C*H*$_3$); LRMS m/z 312.20 (M + H$^+$), calcd C$_{19}$H$_{21}$NO$_3$ 311.1524; HRMS m/z 334.1406 (M + Na$^+$), calcd C$_{19}$H$_{21}$NO$_3$Na$^+$ 334.1419.

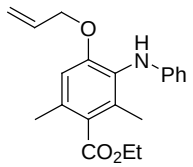
2-methyl-3-phenylamino-4-prop-2-ynyloxy-benzoic acid ethyl ester (109ab):



109ab

Purified by column chromatography using EtOAc/hexane and isolated as a light yellow solid. Mp 60 °C; IR (neat): ν$_{max}$ 3381 (N-*H)*, 3292 (C≡C-*H*), 1714 (O-C=O), 1601, 1504, 1265, 1070, 777, 750 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.80 (1H, d, *J* = 8.8 Hz), 7.18 (2H, t, *J* = 8.0 Hz), 6.96 (1H, d, *J* = 8.4 Hz), 6.83 (1H, t, *J* = 7.2 Hz), 6.62 (2H, d, *J* = 7.6 Hz), 5.70 (1H, s, N-*H*), 4.72 (2H, d, *J* = 2.4 Hz), 4.36 (2H, q, *J* = 6.8 Hz, OC*H*$_2$CH$_3$), 2.46 (1H, t, *J* = 2.4 Hz, OCH$_2$C≡C*H*), 2.42 (3H, s, Ar-C*H*$_3$), 1.39 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 167.5 (C, O-C=O), 154.5 (C), 145.6 (C), 137.7 (C), 130.7 (C), 129.0 (2 x CH), 127.8 (CH), 124.8 (C), 119.4 (CH), 115.1 (2 x CH), 109.4 (CH), 77.8 (C, *C*≡CH), 76.2 (CH, C≡*C*H), 60.6 (CH$_2$, O*C*H$_2$CH$_3$), 56.3 (CH$_2$, O*C*H$_2$C≡CH), 16.4 (CH$_3$, Ar-*C*H$_3$), 14.3 (CH$_3$, OCH$_2$C*H*$_3$); LRMS m/z 310.10 (M + H$^+$), calcd C$_{19}$H$_{19}$NO$_3$ 309.1365; HRMS m/z 332.1268 (M + Na$^+$), calcd C$_{19}$H$_{19}$NO$_3$Na$^+$ 332.1263.

4-Allyloxy-2,6-dimethyl-3-phenylamino-benzoic acid ethyl ester (109ia): Purified by column chromatography using EtOAc/hexane and isolated as a light yellow solid. Mp 42 °C; IR (neat): ν$_{max}$ 3391 (N-*H)*, 2928, 1720 (O-C=O), 1602, 1498, 1265, 1053, 748, 694 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.16 (2H, t, *J* = 7.6 Hz), 6.79 (1H, d, *J* = 7.6 Hz), 6.62 (1H, s), 6.60 (2H, d, *J* = 7.6 Hz), 5.92 (1H, m, OCH$_2$C*H*=CH$_2$), 5.56 (1H, s, N-*H*), 5.25 (1H, br d, *J*

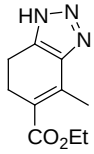


109ia

= 17.6 Hz), 5.19 (1H, br d, *J* = 17.6 Hz) [$OCH_2CH=CH_2$]; 4.49 (2H, m), 4.38 (2H, q, *J* = 7.2 Hz, OCH_2CH_3), 2.33 (3H, s, Ar-CH_3), 2.15 (3H, s, Ar-CH_3), 1.38 (3H, t, *J* =7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 169.8 (C, O-C=O), 153.4 (C), 146.2 (C), 132.8 (CH), 132.2 (C), 128.9 (2 x CH), 128.8 (C), 127.9 (C), 127.7 (C), 119.0 (CH), 117.4 (CH_2, $CH=CH_2$), 114.9 (2 x CH), 111.9 (CH), 69.2 (CH_2, $OCH_2CH=CH_2$), 60.9 (CH_2, OCH_2CH_3), 20.0 (CH_3, Ar-CH_3), 15.6 (CH_3, Ar-CH_3), 14.3 (CH_3, OCH_2CH_3); LRMS m/z 326.25 (M + H^+), calcd $C_{20}H_{23}NO_3$ 325.1680; HRMS m/z 326.1769 (M + H^+), calcd $C_{20}H_{23}NO_3H^+$ 326.1756.

5a: Amino acid-catalyzed cascade [3+2]-CA/H reactions: In an ordinary glass vial equipped with a magnetic stirring bar, to 1.0 mmol of the Hagemann's esters **88** was added 1.0 mL of solvent, and then the catalyst proline **14a** (0.1 mmol, 20-mol%) was added and the reaction mixture was stirred at 25 °C for the 0.25 h; then 0.5 mmol of TsN_3 **118a** was added in one-portion and the reaction mixture was stirred at 25 °C for the time indicated in Tables 18 and 20. The crude reaction mixture was worked up with aqueous NH_4Cl solution and the aqueous layer was extracted with dichloromethane (2 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure cascade products **120**/**121** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

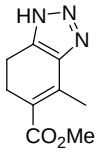
4-Methyl-6,7-dihydro-1H-benzotriazole-5-carboxylic acid ethyl ester (121aa):



121aa

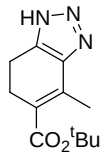
Purified by column chromatography using EtOAc/hexane and isolated as a white solid. Mp 80 °C; IR (neat): ν_{max} 3183 (N-*H*), 3054, 2978, 2903, 1703 (O-C=O), 1609, 1530, 1368, 1294, 1055, 866 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 13.25 (1H, s, N-*H*), 4.29 (2H, q, *J* = 7.2 Hz, OCH_2CH_3), 2.96-2.92 (2H, m), 2.86-2.81 (2H, m), 2.52 (3H, br s, olefinic-CH_3), 1.36 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 168.2 (C, O-C=O), 145.2 (C), 144.1 (C), 136.2 (C), 125.5 (C), 60.6 (CH_2, OCH_2CH_3), 25.6 (CH_2), 19.2 (CH_2), 15.4 (CH_3, olefinic-CH_3), 14.3 (CH_3, OCH_2CH_3); LRMS m/z 208.05 (M + H^+), calcd $C_{10}H_{13}N_3O_2$ 207.1008;

Anal. calcd for $C_{10}H_{13}N_3O_2$ (207.10): C, 57.96; H, 6.32; N, 20.28. Found: C, 57.945; H, 6.325; N, 20.356%.


121sa

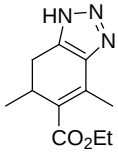
4-Methyl-6,7-dihydro-1H-benzotriazole-5-carboxylic acid methyl ester (121sa): Purified by column chromatography using EtOAc/hexane and isolated as a white solid. Mp 88 °C; IR (neat): ν_{max} 3176 (N-*H*), 2952, 1709 (O-C=O), 1692, 1679, 1607, 1433, 1294, 1232, 1212, 1056 cm^{-1}; ^1H NMR ($CDCl_3$) δ 13.58 (1H, s, N-*H*), 3.83 (3H, s, OC*H*$_3$), 2.96-2.92 (2H, m), 2.85-2.81 (2H, m), 2.52 (3H, br s, olefinic-C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 168.6 (C, O-C=O), 145.2 (C), 144.2 (C), 136.8 (C), 125.1 (C), 51.7 (CH_3, O*C*H$_3$), 25.6 (CH_2), 19.2 (CH_2), 15.5 (CH_3, olefinic-*C*H$_3$); LRMS m/z 194.00 ($M + H^+$), calcd $C_9H_{11}N_3O_2$ 193.0851; HRMS m/z 216.0745 ($M + Na^+$), calcd $C_9H_{11}N_3O_2Na^+$ 216.0749; Anal. calcd for $C_9H_{11}N_3O_2$ (193.08): C, 55.95; H, 5.74; N, 21.75. Found: C, 55.925; H, 5.802; N, 20.872%.

4-Methyl-6,7-dihydro-1H-benzotriazole-5-carboxylic acid tert-butyl ester (121ba):


121ba

Purified by column chromatography using EtOAc/hexane and isolated as a white solid. Mp 68 °C; IR (neat): ν_{max} 3180 (N-*H*), 2975, 1692 (O-C=O), 1453, 1367, 1347, 1299, 1241, 1160, 1053 cm^{-1}; ^1H NMR ($CDCl_3$) δ 12.97 (1H, s, N-*H*), 2.92 (2H, br t, *J* = 8.0 Hz), 2.78 (2H, br t, *J* = 8.0 Hz), 2.46 (3H, br s, olefinic-C*H*$_3$), 1.56 (9H, s, 3 x C*H*$_3$, O-C(*CH*$_3$)$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.7 (C, O-C=O), 145.4 (C), 144.2 (C), 134.3 (C), 127.4 (C), 81.2 (C, O-*C*(CH$_3$)$_3$), 28.3 (3 x CH_3, O-C(*C*H$_3$)$_3$), 25.9 (CH_2), 19.3 (CH_2), 15.3 (CH_3, olefinic-*C*H$_3$); LRMS m/z 236.00 ($M + H^+$), calcd $C_{12}H_{17}N_3O_2$ 235.1321; Anal. calcd for $C_{12}H_{17}N_3O_2$ (235.13): C, 61.26; H, 7.28; N, 17.86. Found: C, 61.268; H, 7.252; N, 17.683%.

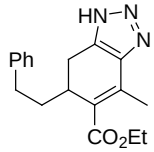
4,6-Dimethyl-6,7-dihydro-1H-benzotriazole-5-carboxylic acid ethyl ester (121ia):


121ia

Purified by column chromatography using EtOAc/hexane and isolated as a liquid. IR (neat): ν_{max} 3185 (N-*H*), 2974, 1703 (O-C=O), 1692, 1678, 1666, 1295, 1197, 1045 cm^{-1}; ^1H NMR ($CDCl_3$) δ 13.25 (1H, s, N-*H*), 4.30 (2H,

q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 3.29-3.25 (1H, m), 3.03 (1H, dd, *J* = 16.0, 7.2 Hz), 2.83 (1H, dd, *J* = 16.0, 1.6 Hz), 2.50 (3H, s, olefinic-C*H*$_3$), 1.36 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$), 1.06 (3H, d, *J* = 7.2 Hz, CHC*H*$_3$); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 168.1 (C, O-C=O), 144.5 (C), 143.0 (C), 134.9 (C), 131.4 (C), 60.6 (CH$_2$, O*C*H$_2$CH$_3$), 30.9 (CH), 26.8 (CH$_2$), 20.0 (CH$_3$, CH*C*H$_3$), 15.3 (CH$_3$, olefinic-*C*H$_3$), 14.3 (CH$_3$, OCH$_2$*C*H$_3$); LRMS m/z 222.05 (M + H$^+$), calcd $C_{11}H_{15}N_3O_2$ 221.1164; Anal. calcd for $C_{11}H_{15}N_3O_2$ (221.11): C, 59.71; H, 6.83; N, 18.99. Found: C, 59.629; H, 6.874; N, 18.667%.

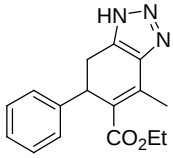
4-Methyl-6-phenethyl-6,7-dihydro-1H-benzotriazole-5-carboxylic acid ethyl ester



121la

(121la): Purified by column chromatography using EtOAc/hexane and isolated as a colorless liquid. IR (neat): ν$_{max}$ 3193 (N-*H*), 2910, 1698 (O-C=O), 1305, 1224, 1053, 980, 698 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 12.82 (1H, s, N-*H*), 7.26-7.21 (2H, m), 7.16-7.11 (3H, m), 4.25 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 3.22-3.20 (1H, m), 3.10 (1H, dd, *J* = 16.4, 1.6 Hz), 2.96 (1H, dd, *J* = 16.4, 6.8 Hz), 2.71-2.66 (1H, m), 2.58-2.52 (1H, m), 2.51 (3H, s, olefinic-C*H*$_3$), 1.80-1.77 (1H, m), 1.61-1.58 (1H, m), 1.31 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 168.0 (C, O-C=O), 144.9 (C), 143.3 (C), 141.6 (C), 135.6 (C), 130.6 (C), 128.3 (4 x CH), 125.8 (CH), 60.6 (CH$_2$, O*C*H$_2$CH$_3$), 35.3 (CH), 34.8 (CH$_2$), 33.1 (CH$_2$), 23.4 (CH$_2$), 15.7 (CH$_3$, olefinic-*C*H$_3$), 14.2 (CH$_3$, OCH$_2$*C*H$_3$); LRMS m/z 312.05 (M + H$^+$), calcd $C_{18}H_{21}N_3O_2$ 311.1634; HRMS m/z 312.1697 (M + H$^+$), calcd $C_{18}H_{21}N_3O_2H^+$ 312.1712; Anal. calcd for $C_{18}H_{21}N_3O_2$ (311.16): C, 69.43; H, 6.80; N, 13.49. Found: C, 69.490; H, 6.832; N, 13.869%.

4-Methyl-6-phenyl-6,7-dihydro-1H-benzotriazole-5-carboxylic acid ethyl ester

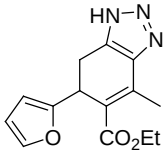


121ma

(121ma): Purified by column chromatography using EtOAc/hexane and isolated as a gummy liquid; IR (neat): ν$_{max}$ 3183 (N-*H*), 2979, 1697 (O-C=O), 1307, 1269, 1225, 1053, 756, 699 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 12.91 (1H, s, N-*H*), 7.20-7.14 (3H, m), 7.07 (2H, d, *J* = 6.8 Hz), 4.46 (1H, br d, *J* = 7.6 Hz), 4.13 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 3.35 (1H, dd, *J* = 16.4, 8.4 Hz), 3.12 (1H, dd, *J* = 16.4, 2.8 Hz), 2.61 (3H, s, olefinic-C*H*$_3$), 1.17 (3H, t, *J* = 7.2 Hz,

OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.7 (C, O-C=O), 145.2 (C), 142.8 (C), 136.4 (C), 128.5 (2 x CH), 127.1 (2 x CH), 126.7 (CH), 60.6 (CH_2, OCH_2CH_3), 41.6 (CH), 28.3 (CH_2), 15.6 (CH_3, olefinic-CH_3), 14.0 (CH_3, OCH_2CH_3) [2 quaternary carbons in the triazole ring are poor resolution even after more scans, may be due to the resonance]; LRMS m/z 284.00 (M + H^+), calcd $C_{16}H_{17}N_3O_2$ 283.1321; HRMS m/z 284.1364 (M + H^+) and 306.1220 (M + Na^+), calcd $C_{16}H_{17}N_3O_2H^+$ 284.1399 and $C_{16}H_{17}N_3O_2Na^+$ 306.1219; Anal. calcd for $C_{16}H_{17}N_3O_2$ (283.13): C, 67.83; H, 6.05; N, 14.83. Found: C, 67.836; H, 6.080; N, 14.654%.

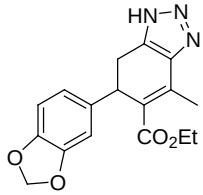
6-Furan-2-yl-4-methyl-6,7-dihydro-1H-benzotriazole-5-carboxylic acid ethyl ester



121ra

(121ra): Purified by column chromatography using EtOAc/hexane and isolated as a yellow liquid; IR (neat): ν_{max} 3179 (N-*H*), 2979, 2904, 1703 (O-C=O), 1692, 1678, 1291, 1223, 1170, 1052, 736 cm^{-1}; ^1H NMR ($CDCl_3$) δ 12.78 (1H, s, N-*H*), 7.22 (1H, s), 6.12 (1H, d, *J* = 1.6 Hz), 5.84 (1H, d, *J* = 2.8 Hz), 4.60 (1H, br d, *J* = 7.2 Hz), 4.26 (2H, q, *J* = 7.2 Hz, OCH_2CH_3), 3.38 (1H, br d, *J* = 16.4 Hz), 3.16 (1H, dd, *J* = 16.4, 7.2 Hz), 2.60 (3H, s, olefinic-CH_3), 1.30 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.4 (C, O-C=O), 155.2 (C), 144.9 (C), 142.7 (C), 141.6 (CH), 138.0 (C), 125.9 (C), 109.9 (CH), 105.8 (CH), 60.8 (CH_2, OCH_2CH_3), 35.2 (CH), 24.9 (CH_2), 15.8 (CH_3, olefinic-CH_3), 14.2 (CH_3, OCH_2CH_3); LRMS m/z 274.05 (M + H^+), calcd $C_{14}H_{15}N_3O_3$ 273.1113; Anal. calcd for $C_{14}H_{15}N_3O_3$ (273.11): C, 61.53; H, 5.53; N, 15.38. Found: C, 61.438; H, 5.583; N, 15.398%.

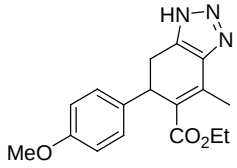
6-Benzo[1,3]dioxol-5-yl-4-methyl-6,7-dihydro-1H-benzotriazole-5-carboxylic acid ethyl ester (121oa): Purified by column chromatography using EtOAc/hexane and isolated as a yellow gummy liquid; IR (neat): ν_{max} 3241 (N-*H*), 2978, 2900, 1703 (O-C=O), 1485, 1441, 1368, 1290, 1228, 1122, 1095, 1039, 974, 81l cm^{-1}; ^1H NMR ($CDCl_3$) δ 12.87 (1H, s, N-*H*), 6.62 (1H, d, *J* = 8.0 Hz), 6.56-6.54 (2H, m), 5.86 (2H, d, *J* = 1.6 Hz, OCH_2O), 4.40 (1H, br d, *J* = 7.6 Hz, ArC*H*), 4.16 (2H, q, *J* = 7.2 Hz, OCH_2CH_3), 3.32



121oa

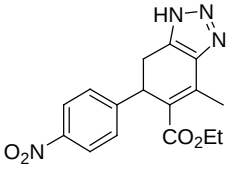
(1H, dd, *J* = 16.4, 8.4 Hz), 3.09 (1H, dd, *J* = 16.4, 2.8 Hz), 2.60 (3H, s, olefinic-C*H*$_3$), 1.23 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 167.6 (C, O-C=O), 147.6 (C), 146.3 (C), 145.1 (C), 142.3 (C), 136.7 (C), 136.4 (C), 128.6 (C), 120.2 (CH), 108.2 (CH), 107.6 (CH), 100.8 (CH$_2$, O*C*H$_2$O), 60.7 (CH$_2$, O*C*H$_2$CH$_3$), 41.2 (CH), 28.4 (CH$_2$), 15.7 (CH$_3$, olefinic-*C*H$_3$), 14.1 (CH$_3$, OCH$_2$*C*H$_3$); LRMS m/z 328.00 (M + H$^+$), calcd $C_{17}H_{17}N_3O_4$ 327.1219; HRMS m/z 328.1293 (M + H$^+$), calcd $C_{17}H_{17}N_3O_4H^+$ 328.1297; Anal. calcd for $C_{17}H_{17}N_3O_4$ (327.12): C, 62.38; H, 5.23; N, 12.84. Found: C, 62.412; H, 5.225; N, 12.872%.

6-(4-Methoxy-phenyl)-4-methyl-6,7-dihydro-1H-benzotriazole-5-carboxylic acid ethyl ester (121na): Purified by column chromatography using EtOAc/hexane and isolated as a liquid; IR (neat): ν_{max} 3190 (N-*H*), 2977, 1697 (O-C=O), 1606, 1510, 1462, 1303, 1225, 1179, 1034, 832, 735 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 12.94 (1H, s, N-*H*), 6.99 (2H, d, *J* = 8.4 Hz), 6.72 (2H, d, *J* = 8.4 Hz), 4.42 (1H, br d, *J* = 6.8 Hz), 4.14 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 3.72 (3H, s, OC*H*$_3$), 3.32 (1H, dd, *J* = 16.4, 8.4 Hz), 3.09 (1H, dd, *J* = 16.4, 2.4 Hz), 2.60 (3H, s, olefinic-C*H*$_3$), 1.20 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 167.8 (C, O-C=O), 158.3 (C), 145.2 (C), 142.2 (C), 136.0 (C), 134.9 (C), 128.9 (C), 128.1 (2 x CH), 113.9 (2 x CH), 60.6 (CH$_2$, O*C*H$_2$CH$_3$), 55.1 (CH$_3$, O*C*H$_3$), 40.8 (CH), 28.4 (CH$_2$), 15.6 (CH$_3$, olefinic-*C*H$_3$), 14.1 (CH$_3$, OCH$_2$*C*H$_3$); LRMS m/z 314.00 (M + H$^+$), calcd $C_{17}H_{19}N_3O_3$ 313.1426; HRMS m/z 336.1276 (M + Na$^+$) and 314.1465 (M + H$^+$), calcd $C_{17}H_{19}N_3O_3Na^+$ 336.1324 and $C_{17}H_{19}N_3O_3H^+$ 314.1505; Anal. calcd for $C_{17}H_{19}N_3O_3$ (313.14): C, 65.16; H, 6.11; N, 13.41. Found: C, 65.140; H, 6.142; N, 13.631%.



121na

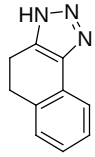
4-Methyl-6-(4-nitro-phenyl)-6,7-dihydro-1H-benzotriazole-5-carboxylic acid ethyl ester (121qa): Purified by column chromatography using EtOAc/hexane and isolated as a yellow liquid; IR (neat): ν_{max} 3201 (N-*H*), 2978, 1696 (O-C=O), 1601, 1519, 1463, 1346, 1312, 1268,



121qa

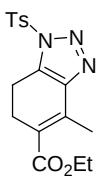
1226, 1053, 1017, 856 cm^{-1}; ^1H NMR ($CDCl_3$) δ 12.61 (1H, s, N-*H*), 8.06 (2H, d, *J* = 8.8 Hz), 7.24 (2H, d, *J* = 8.8 Hz), 4.58 (1H, br d, *J* = 7.6 Hz), 4.16 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 3.41 (1H, dd, *J* = 16.4, 8.4 Hz), 3.11 (1H, dd, *J* = 16.8, 2.4 Hz), 2.66 (3H, s, olefinic-C*H*$_3$), 1.21 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.2 (C, O-C=O), 150.4 (C), 146.9 (C), 145.1 (C), 142.0 (C), 138.4 (C), 128.0 (2 x CH), 127.0 (C), 123.9 (2 x CH), 60.9 (CH_2, O*C*H$_2$CH$_3$), 41.4 (CH), 27.9 (CH_2), 15.8 (CH_3, olefinic-*C*H$_3$), 14.1 (CH_3, OCH$_2$*C*H$_3$); LRMS m/z 329.00 (M + H^+), calcd $C_{16}H_{16}N_4O_4$ 328.1172; HRMS m/z 329.1258 (M + H^+), calcd $C_{16}H_{16}N_4O_4H^+$ 329.1250; Anal. calcd for $C_{16}H_{16}N_4O_4$ (328.11): C, 58.53; H, 4.91; N, 17.06. Found: C, 58.411; H, 4.914; N, 16.889%.

4,5-Dihydro-3H-naphtho[1,2-*d*][1,2,3]triazole (121ua): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 112 °C; IR (neat): ν_{max} 3037 (N-*H*), 2941, 2915, 2847, 2740, 2581, 1187, 1009, 768 cm^{-1}; ^1H NMR ($CDCl_3$) δ 12.86 (1H, s, N-*H*), 7.87 (1H, d, *J* = 7.6 Hz), 7.34-7.26 (3H, m), 3.12-3.03 (4H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 144.0 (C), 143.1 (C), 136.1 (C), 128.6 (CH), 128.4 (CH), 127.4 (C), 127.2 (CH), 123.0 (CH), 29.1 (CH_2), 20.0 (CH_2); LRMS m/z 172.00 (M + H^+), calcd $C_{10}H_9N_3$ 171.0796; Anal. calcd for $C_{10}H_9N_3$ (171.07): C, 70.16; H, 5.30; N, 24.54. Found: C, 70.163; H, 5.296; N, 24.481%.

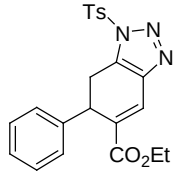


121ua

4-Methyl-1-(toluene-4-sulfonyl)-6,7-dihydro-1H-benzotriazole-5-carboxylic acid ethyl ester (120aa): Purified by column chromatography using EtOAc/hexane and isolated as a white solid. Mp 106 °C; IR (neat): ν_{max} 1703 (O-C=O), 1610, 1385, 1278, 1207, 1192, 1054, 808 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.98 (2H, d, *J* = 8.0 Hz), 7.39 (2H, d, *J* = 7.6 Hz), 4.25 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 3.16 (2H, br t, *J* = 8.8 Hz), 2.84 (2H, br t, *J* = 8.4 Hz), 2.51 (3H, s, olefinic-C*H*$_3$), 2.45 (3H, s, Ar-C*H*$_3$), 1.33 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.5 (C, O-C=O), 147.3 (C), 145.3 (C), 136.9 (C), 135.1 (C), 133.5 (C),



120aa

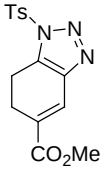


120fa

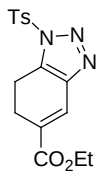
130.5 (2 x CH), 128.5 (2 x CH), 122.4 (C), 60.6 (CH_2, O*C*H_2CH_3), 25.0 (CH_2), 21.8 (CH_3, Ar-*C*H_3), 19.7 (CH_2), 15.1 (CH_3, olefinic-*C*H_3), 14.3 (CH_3, OCH_2*C*H_3); LRMS m/z 362.00 (M + H^+), calcd $C_{17}H_{19}N_3O_4S$ 361.1096; Anal. calcd for $C_{17}H_{19}N_3O_4S$ (361.10): C, 56.49; H, 5.30; N, 11.63. Found: C, 56.450; H, 5.294; N, 11.612%.

6-Phenyl-1-(toluene-4-sulfonyl)-6,7-dihydro-1H-benzotriazole-5-carboxylic acid ethyl ester (120fa): Purified by column chromatography using EtOAc/hexane and isolated as a yellow liquid; IR (neat): ν_{max} 2924, 1712 (O-C=O), 1371, 1297, 1229, 1161, 1121, 1030, 1008, 816 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.87 (1H, s, olefinic-*H*), 7.63 (2H, d, *J* = 8.0 Hz), 7.21-7.13 (5H, m, Ph-*H*), 7.02 (2H, d, *J* = 7.2 Hz), 4.46 (1H, br d, *J* = 8.8 Hz, PhC*H*), 4.17 (2H, m, OC*H*$_2$CH$_3$), 3.66 (1H, br d, *J* = 18.0 Hz), 3.54 (1H, br dd, *J* = 18.0, 9.2 Hz), 2.40 (3H, s, Ar-C*H*$_3$), 1.24 (3H, t, *J* = 7.2 Hz, OCH_2C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 165.6 (C, O-C=O), 147.0 (C), 142.7 (C), 140.9 (C), 134.6 (C), 133.4 (C), 131.7 (C), 130.4 (2 x CH), 128.8 (2 x CH), 128.0 (2 x CH), 127.2 (CH), 127.0 (CH), 126.6 (2 x CH), 61.1 (CH_2, O*C*H_2CH_3), 38.9 (CH), 29.3 (CH_2), 21.8 (CH_3, Ar-*C*H_3), 14.1 (CH_3, OCH_2*C*H_3); Anal. calcd for $C_{22}H_{21}N_3O_4S$ (423.13): C, 62.40; H, 5.00; N, 9.92. Found: C, 62.395; H, 5.050; N, 10.055%.

1-(Toluene-4-sulfonyl)-6,7-dihydro-1H-benzotriazole-5-carboxylic acid methyl ester (120ta): Purified by column chromatography using EtOAc/hexane and isolated as a white solid. Mp 134 °C; IR (neat): ν_{max} 2953, 1711 (O-C=O), 1434, 1395, 1295, 1201, 1194, 1184, 1093, 681 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.99 (2H, d, *J* = 8.4 Hz), 7.60 (1H, s, olefinic-*H*), 7.40 (2H, d, *J* = 8.4 Hz), 3.81 (3H, s, OC*H*$_3$), 3.26 (2H, t, *J* = 9.2 Hz), 2.87 (2H, dt, *J* = 9.2, 1.6 Hz), 2.46 (3H, s, Ar-C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 166.6 (C, O-C=O), 147.4 (C), 142.5 (C), 135.8 (C), 133.4 (C), 130.5 (2 x CH), 128.6 (2 x CH), 128.2 (C), 126.7 (CH), 52.1 (CH_3, O*C*H_3), 22.8 (CH_2), 21.8 (CH_3, Ar-*C*H_3), 19.7 (CH_2); LRMS m/z 334.00 (M + H^+), calcd $C_{15}H_{15}N_3O_4S$ 333.0783; Anal. calcd for $C_{15}H_{15}N_3O_4S$ (333.07): C, 54.04; H, 4.54; N, 12.60. Found: C, 54.076; H, 4.526; N, 12.576%.



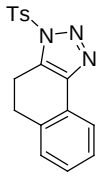
120ta



120ea

1-(Toluene-4-sulfonyl)-6,7-dihydro-1H-benzotriazole-5-carboxylic acid ethyl ester (120ea): Purified by column chromatography using EtOAc/hexane and isolated as a white solid. Mp 102 °C; IR (neat): ν_{max} 2929, 1703 (O-C=O), 1447, 1395, 1336, 1295, 1200, 1194, 1184, 1094, 1069, 735, 681 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.91 (2H, d, *J* = 8.4 Hz), 7.52 (1H, t, *J* = 1.6 Hz, olefinic-*H*), 7.33 (2H, d, *J* = 8.0 Hz), 4.18 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 3.18 (2H, t, *J* = 9.2 Hz), 2.79 (2H, dt, *J* = 9.2, 1.6 Hz), 2.39 (3H, s, Ar-C*H*$_3$), 1.25 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 166.1 (C, O-C=O), 147.4 (C), 142.5 (C), 135.8 (C), 133.4 (C), 130.5 (2 x CH), 128.5 (2 x CH and C), 126.4 (CH), 61.0 (CH_2, O*C*H$_2$CH$_3$), 22.8 (CH_2), 21.8 (CH_3, Ar-*C*H$_3$), 19.7 (CH_2), 14.2 (CH_3, OCH$_2$*C*H$_3$); LRMS m/z 348.00 (M + H^+), calcd $C_{16}H_{17}N_3O_4S$ 347.0940; Anal. calcd for $C_{16}H_{17}N_3O_4S$ (347.09): C, 55.32; H, 4.93; N, 12.10. Found: C, 55.278; H, 4.951; N, 12.495%.

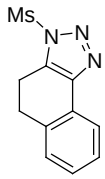
3-(Toluene-4-sulfonyl)-4,5-dihydro-3H-naphtho[1,2-*d*][1,2,3]triazole (120ua):



120ua

Purified by column chromatography using EtOAc/hexane and isolated as a white solid. Mp 140 °C; IR (neat): ν_{max} 2924, 1589, 1446, 1389, 1339, 1195, 1172, 1121, 994 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.98 (2H, d, *J* = 8.4 Hz), 7.90 (1H, d, *J* = 7.2 Hz), 7.37 (2H, d, *J* = 8.0 Hz), 7.28-7.22 (3H, m), 3.27 (2H, t, *J* = 7.6 Hz), 3.09 (2H, t, *J* = 7.6 Hz), 2.43 (3H, s, Ar-C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 147.0 (C), 143.6 (C), 133.8 (C), 133.7 (C), 133.4 (C), 130.4 (2 x CH), 128.4 (2 x CH), 128.3 (CH), 128.1 (CH), 127.3 (CH), 127.1 (C), 122.5 (CH), 28.0 (CH_2), 21.8 (CH_3, Ar-*C*H$_3$), 20.1 (CH_2); LRMS m/z 326.00 (M + H^+), calcd $C_{17}H_{15}N_3O_2S$ 325.0885; Anal. calcd for $C_{17}H_{15}N_3O_2S$ (325.08): C, 62.75; H, 4.65; N, 12.91. Found: C, 62.740; H, 4.644; N, 12.999%.

3-Methanesulfonyl-4,5-dihydro-3H-naphtho[1,2-*d*][1,2,3]triazole (120ub): Purified



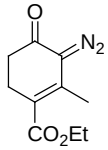
120ub

by column chromatography using EtOAc/hexane and isolated as a white solid. Mp 124 °C; IR (neat): ν_{max} 3018, 2933, 1384, 1371, 1340, 1333, 1195, 1180, 1008, 975, 956, 779, 764 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.92 (1H, d, *J* = 7.6

Hz), 7.31-7.24 (3H, m), 3.56 (3H, s, SO_2CH_3), 3.25 (2H, t, *J* = 7.6 Hz), 3.10 (2H, t, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 143.5 (C), 134.1 (C), 133.5 (C), 128.5 (CH), 128.2 (CH), 127.3 (CH), 126.7 (C), 122.4 (CH), 43.0 (CH_3, SO_2CH_3), 27.9 (CH_2), 19.9 (CH_2); LRMS m/z 250.00 ($M + H^+$), calcd $C_{11}H_{11}N_3O_2S$ 249.0572; Anal. calcd for $C_{11}H_{11}N_3O_2S$ (249.05): C, 53.00; H, 4.45; N, 16.86. Found: C, 53.008; H, 4.453; N, 16.937%.

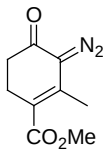
5b: Amine-catalyzed cascade EA/E reactions: In an ordinary glass vial equipped with a magnetic stirring bar, to 0.12 mmol of the $BnNH_2$ **2d**, and 0.3 mmol of Hagemann's esters **88** was added 0.5 mL of solvent, and then the 0.5 mL solution of TsN_3 **118a** (0.3 mmol) was added dropwise for 0.5 h and the reaction mixture was stirred at 25 °C for the time indicated in Tables 17 and 21. The crude reaction mixture was worked up with aqueous NH_4Cl solution and the aqueous layer was extracted with dichloromethane (2 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure cascade products **119** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

3-Diazo-2-methyl-4-oxo-cyclohex-1-enecarboxylic acid ethyl ester (119aa): Purified by column chromatography using EtOAc/hexane and isolated as a yellow solid. Mp 34 °C; IR (neat): ν_{max} 2982, **2091 (diazo)**, 1699 (O-C=O), 1661, 1603, 1447, 1370, 1260, 1173, 1047, 864 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.22 (2H, q, *J* = 7.2Hz, OCH_2CH_3), 2.76 (2H, t, *J* = 6.8 Hz), 2.54 (2H, t, *J* = 6.8 Hz), 2.32 (3H, s, olefinic-CH_3), 1.32 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 192.7 (C, C=O), 166.3 (C, O-C=O), 133.8 (C), 116.7 (C), 60.4 (CH_2, OCH_2CH_3), 36.3 (CH_2), 23.8 (CH_2), 16.3 (CH_3, olefinic-CH_3), 14.3 (CH_3, OCH_2CH_3) [one of the quaternary carbon attached to the diazo group is poor resolution even after more scans, may be due to the resonance]; Anal. calcd for $C_{10}H_{12}N_2O_3$ (208.08): C, 57.68; H, 5.81; N, 13.45. Found: C, 57.597; H, 5.795; N, 13.578%.



119aa

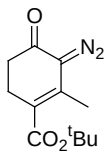
3-Diazo-2-methyl-4-oxo-cyclohex-1-enecarboxylic acid methyl ester (119sa):



119sa

Purified by column chromatography using EtOAc/hexane and isolated as a yellow solid. Mp 50 °C; IR (neat): ν_{max} 3000, **2088 (diazo)**, 1696 (O-C=O), 1662, 1598, 1435, 1366, 1259, 1201, 1167, 1139 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.76 (3H, s, OC*H*$_3$), 2.75 (2H, t, *J* = 6.4 Hz), 2.53 (2H, t, *J* = 6.8 Hz), 2.33 (3H, s, olefinic-C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 192.5 (C, C=O), 166.7 (C, O-C=O), 134.3 (C), 116.3 (C), 51.4 (CH_3, O*C*H$_3$), 36.3 (CH_2), 23.8 (CH_2), 16.3 (CH_3, olefinic-*C*H$_3$) [one of the quaternary carbon attached to the diazo group is poor resolution even after more scans, may be due to the resonance]; Anal. calcd for $C_9H_{10}N_2O_3$ (194.07): C, 55.67; H, 5.19; N, 14.43. Found: C, 55.680; H, 5.204; N, 14.608%.

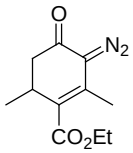
3-Diazo-2-methyl-4-oxo-cyclohex-1-enecarboxylic acid tert-butyl ester (119ba):



119ba

Purified by column chromatography using EtOAc/hexane and isolated as a yellow solid. Mp 40 °C; IR (neat): ν_{max} 2975, **2087 (diazo),** 1691 (O-C=O), 1678, 1665, 1599, 1456, 1366, 1267, 1207, 1157, 1137 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.72–2.68 (2H, m), 2.52 (2H, t, *J* = 7.2 Hz), 2.27 (3H, s, olefinic-C*H*$_3$), 1.52 (9H, s, 3 x C*H*$_3$, *tert*-Bu); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 193.0 (C, C=O), 165.9 (C, O-C=O), 132.0 (C), 118.6 (C), 80.8 [C, O*C*(CH$_3$)$_3$], 36.4 (CH_2), 28.3 [3 x CH_3, OC(*C*H$_3$)$_3$], 24.2 (CH_2), 16.3 (CH_3, olefinic-*C*H$_3$) [one of the quaternary carbon attached to the diazo group is poor resolution even after more scans, may be due to the resonance]; LRMS m/z 237.00 (M + H^+), calcd $C_{12}H_{16}N_2O_3$ 236.1161; Anal. calcd for $C_{12}H_{16}N_2O_3$ (236.12): C, 61.00; H, 6.83; N, 11.86. Found: C, 60.901; H, 6.840; N, 11.941%.

3-Diazo-2,6-dimethyl-4-oxo-cyclohex-1-enecarboxylic acid ethyl ester (119ia):

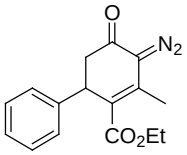


119ia

Purified by column chromatography using EtOAc/hexane and isolated as a yellow liquid. IR (neat): ν_{max} 2976, **2091 (diazo)**, 1693 (O-C=O), 1666, 1596, 1369, 1330, 1292, 1260, 1232, 1193, 1090, 1047 cm^{-1}; ^1H NMR

($CDCl_3$) δ 4.24 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 3.26 -3.23 (1H, m), 2.66 (1H, dd, *J* = 16.0, 6.4 Hz), 2.42 (1H, dd, *J* = 16.4, 2.0 Hz), 2.31 (3H, s, olefinic-C*H*$_3$), 1.33 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$), 1.09 (3H, d, *J* = 6.8 Hz, CHC*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 192.4 (C, C=O), 166.2 (C, O-C=O), 132.5 (C), 122.2 (C), 60.3 (CH_2, O*C*H$_2$CH$_3$), 43.6 (CH_2), 30.1 (CH), 19.6 (CH_3, CH*C*H$_3$), 16.5 (CH_3, olefinic-*C*H$_3$), 14.3 (CH_3, OCH$_2$*C*H$_3$) [one of the quaternary carbon attached to the diazo group is poor resolution even after more scans, may be due to the resonance]; LRMS m/z 223.00 (M + H$^+$), calcd $C_{11}H_{14}N_2O_3$ 222.1004; Anal. calcd for $C_{11}H_{14}N_2O_3$ (222.10): C, 59.45; H, 6.35; N, 12.61. Found: C 59.440; H, 6.320; N, 12.602%.

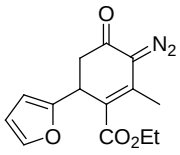
3-Diazo-2-methyl-4-oxo-6-phenyl-cyclohex-1-enecarboxylicacid ethyl ester



119ma

(119ma): Purified by column chromatography using EtOAc/hexane and isolated as a yellow liquid. IR (neat): ν_{max} 2982, 2929, **2091 (diazo)**, 1695 (O-C=O), 1666, 1596, 1369, 1247, 1170, 1137, 741 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.28–7.19 (3H, m), 7.15 (2H, d, *J* = 7.6 Hz), 4.47 (1H, br d, *J* = 7.2 Hz, PhC*H*), 4.13 (2H, q, *J* = 6.8 Hz, OC*H*$_2$CH$_3$), 2.95 (1H, dd, *J* = 16.4, 7.2 Hz), 2.80 (1H, br d, *J* = 16.4 Hz), 2.43 (3H, s, olefinic-C*H*$_3$), 1.19 (3H, t, *J* = 6.8 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 191.3 (C, C=O), 166.1 (C, O-C=O), 142.1 (C), 134.4 (C), 128.7 (2 x CH), 126.9 (CH), 126.8 (2 x CH), 119.7 (C), 60.5 (CH_2, O*C*H$_2$CH$_3$), 44.0 (CH_2), 40.4 (CH), 16.7 (CH_3, olefinic-*C*H$_3$), 14.1 (CH_3, OCH$_2$*C*H$_3$) [one of the quaternary carbon attached to the diazo group is poor resolution even after more scans, may be due to the resonance]; Anal. calcd for $C_{16}H_{16}N_2O_3$ (284.12): C, 67.59; H, 5.67; N, 9.85. Found: C, 67.582; H, 5.701; N, 9.991%.

3-Diazo-6-furan-2-yl-2-methyl-4-oxo-cyclohex-1-enecarboxylic acid ethyl ester



119ra

(119ra): Purified by column chromatography using EtOAc/hexane and isolated as a yellow liquid. IR (neat): ν_{max} 2978, **2092 (diazo)**, 1734 (O-C=O), 1669, 1595, 1369, 1289, 1254, 1176, 1151, 1042, 739 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.27 (1H, d, *J* = 2.8 Hz), 6.23 (1H, t, *J* = 2.8 Hz), 5.98 (1H, d, *J* = 2.8 Hz), 4.56 (1H, br d, *J* = 6.4 Hz), 4.23 (2H, q, *J* = 7.2 Hz,

OC*H*$_2$CH$_3$), 2.92 (1H, dd, *J* = 16.4, 2.0 Hz), 2.81 (1H, dd, *J* = 16.4, 6.8 Hz), 2.39 (3H, s, olefinic-C*H*$_3$), 1.30 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$, DEPT-135) δ 191.0 (C, C=O), 165.7 (C, O-C=O), 154.7 (C), 141.9 (CH), 135.7 (C), 117.1 (C), 110.0 (CH), 105.5 (CH), 60.6 (CH$_2$, O*C*H$_2$CH$_3$), 40.7 (CH$_2$), 34.2 (CH), 16.8 (CH$_3$, olefinic-*C*H$_3$), 14.2 (CH$_3$, OCH$_2$*C*H$_3$) [one of the quaternary carbon attached to the diazo group is poor resolution even after more scans, may be due to the resonance]; LRMS m/z 273.00 (M - H$^+$), calcd C$_{14}$H$_{14}$N$_2$O$_4$ 274.0954; Anal. calcd for C$_{14}$H$_{14}$N$_2$O$_4$ (274.09): C, 61.31; H, 5.14; N, 10.21. Found: C, 61.383; H, 5.184; N, 10.194%.

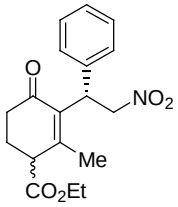
6a: Pyrrolidine-catalyzed Michael reactions: In an ordinary glass vial equipped with a magnetic stirring bar, to 0.5 mmol of the Hagemann's ester **88** was added 1.0 mL of DMSO solvent, and then the catalyst pyrrolidine **2a** (0.1 mmol, 8.19μL) was added and then 0.6 mmol of β-nitrostyrene **35** was added in one-portion and the reaction mixture was stirred at RT for the time indicated in Table 24. The crude reaction mixture was worked up with aqueous NH$_4$Cl solution and the aqueous layer was extracted with dichloromethane (2 x 20 mL). The combined organic layers were dried (Na$_2$SO$_4$), filtered and concentrated. Pure achiral Michael products **133/134** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

6b: (*S*)-Bis-(3,5-dimethylphenyl)-pyrrolidin-2-yl-methanol catalyzed Michael reactions: In an ordinary glass vial equipped with a magnetic stirring bar, to 0.1 mmol of the Hagemann's esters **88** was added 1.0 mL of toluene solvent, and then the catalyst (*S*)-bis-(3,5-dimethylphenyl)-pyrrolidin-2-yl-methanol (*S*)-**2r** (0.03 mmol, 30 mol%), thiourea **132b** (0.03 mmol, 30 mol%) was added and then 0.15 mmol of β-nitrostyrene **35** were added in one-portion and the reaction mixture was stirred at RT for the time indicated in Table 25. The crude reaction mixture was worked up with aqueous NH$_4$Cl solution and the aqueous layer was extracted with dichloromethane (2 x 20 mL). The combined organic layers were dried (Na$_2$SO$_4$), filtered and concentrated. Pure chiral

Michael products **133/134** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

6c: (*R*)-Bis-(3,5-dimethylphenyl)-pyrrolidin-2-yl-methanol catalyzed Michael reactions: In an ordinary glass vial equipped with a magnetic stirring bar, to 0.1 mmol of the Hagemann's esters **88a** & **88b** was added 1.0 mL of toluene solvent and then the catalyst (*R*)-bis-(3,5-dimethylphenyl)-pyrrolidin-2-yl-methanol **2r** (0.03 mmol, 30 mol%), thiourea **132b** (0.03 mmol, 30 mol%) was added and then 0.15 mmol of β-nitrostyrene **35a** were added in one-portion and the reaction mixture was stirred at RT for the time indicated in Table 4. The crude reaction mixture was worked up with aqueous NH_4Cl solution and the aqueous layer was extracted with dichloromethane (2 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure chiral Michael products (+)-**133aa/134aa** and (–)-**133ba/134ba** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

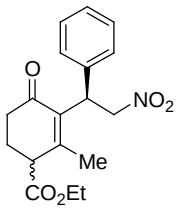
(*S*,*S*)-2-Methyl-3-(2-nitro-1-phenylethyl)-4-oxo-cyclohex-2-enecarboxylic acid ethyl ester (133aa) and (*S*,*R*)-2-Methyl-3-(2-nitro-1-phenylethyl)-4-oxo-cyclohex-2-enecarboxylic acid ethyl ester (134aa): Prepared following the procedure **6b** and purified by column chromatography using EtOAc/hexane and isolated as a colorless liquid. The ee was determined by chiral-phase HPLC using a Daicel Chiralcel OD-H column (hexane/*i*-PrOH = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 14.3 min (minor), t_R = 17.2 min (major), t_R = 20.8 min (major), t_R = 25.5 min (minor); **$[\alpha]^{25}_D$ = +9.5 (*c* 0.3, $CHCl_3$, 70% ee, –7% ee)**; IR (neat): ν_{max} 2965, 1727 (O-C=O), 1666 (C=O), 1551, 1375, 1160, 857, 700 and 625 cm^{-1}; ^1H NMR ($CDCl_3$, 1.3:1 ratio of diastereomers) δ 7.32-7.28 (4H, m), 7.25-7.21 (6H, m), 5.30 (1H, dd, *J* = 12.4, 9.2 Hz), 5.18 (2H, br d, *J* = 7.6 Hz), 5.08 (1H, dd, *J* = 12.4, 6.0 Hz), 4.85 (1H, t, *J* = 7.6 Hz), 4.79 (1H, dd, *J* = 8.8, 6.0 Hz), 4.22 (2H, q, *J* = 7.2 Hz, OCH_2CH_3), 4.19 (2H, q, *J* = 7.2 Hz, OCH_2CH_3), 3.37 (1H, t, *J* = 4.4 Hz), 3.34 (1H, t, *J* = 4.4 Hz), 2.62-2.50 (1H, m), 2.47 (1H, dd, *J* = 12.0, 5.6 Hz), 2.42 (1H, t, *J* = 4.8 Hz), 2.37 (1H, t, *J* = 4.0 Hz), 2.34-2.20 (4H, m), 2.16



133aa/134aa
dr = 1.3:1

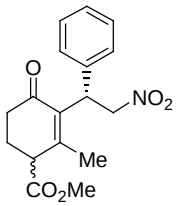
(3H, s, olefinic-CH_3), 2.13 (3H, s, olefinic-CH_3), 1.30 (3H, t, J = 7.2 Hz, OCH_2CH_3), 1.25 (3H, t, J = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135, 1.3:1 ratio of diastereomers) δ 197.4 (C, C=O), 197.1 (C, C=O), 171.4 (C, O-C=O), 171.3 (C, O-C=O), 155.1 (C), 154.8 (C), 138.5 (C), 138.2 (C), 135.3 (C), 135.0 (C), 128.7 (2 x CH), 128.6 (2 x CH), 127.5 (2 x CH), 127.1 (CH), 127.0 (3 x CH), 77.60 (CH_2), 77.57 (CH_2), 61.6 (CH_2, OCH_2CH_3), 61.4 (CH_2, OCH_2CH_3), 48.4 (CH), 48.3 (CH), 42.0 (CH), 41.9 (CH), 35.3 (CH_2), 35.2 (CH_2), 25.2 (CH_2), 25.1 (CH_2), 21.2 (CH_3, olefinic-CH_3), 21.1 (CH_3, olefinic-CH_3), 14.04 (CH_3, OCH_2CH_3), 14.02 (CH_3, OCH_2CH_3); LRMS m/z 332.00 ($M + H^+$), calcd $C_{18}H_{21}NO_5$ 331.1420; Anal. calcd for $C_{18}H_{21}NO_5$ (331.14): C, 65.24; H, 6.39; N, 4.23. Found: C, 65.31; H, 6.35; N, 4.26%.

(*R*,*S*)-2-Methyl-3-(2-nitro-1-phenylethyl)-4-oxo-cyclohex-2-enecarboxylic acid ethyl ester (133aa) and (*R*,*R*)-2-Methyl-3-(2-nitro-1-phenylethyl)-4-oxo-cyclohex-2-enecarboxylic acid ethyl ester (134aa): Prepared following the procedure **6c** and purified by column chromatography using EtOAc/hexane and isolated as a colorless liquid. The ee was determined by chiral-phase HPLC using a Daicel Chiralcel OD-H column (hexane/*i*-PrOH = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 14.3 min (minor), t_R = 17.2 min (major), t_R = 21.2 min (minor), t_R = 25.4 min (major); **$[\alpha]^{25}_D$ = +3.5 (*c* 0.3, $CHCl_3$, –70% ee, –14% ee)**; IR (neat): ν_{max} 2965, 1727 (O-C=O), 1666 (C=O), 1551, 1375, 1160, 857, 700 and 625 cm^{-1}.



(+)-**133aa/134aa**
dr = 1.2:1

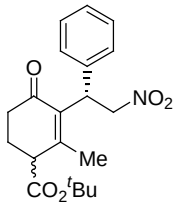
(*S*,*S*)-2-Methyl-3-(2-nitro-1-phenylethyl)-4-oxo-cyclohex-2-enecarboxylic acid methyl ester (133sa) and (*S*,*R*)-2-Methyl-3-(2-nitro-1-phenylethyl)-4-oxo-cyclohex-2-enecarboxylic acid methyl ester (134sa): Prepared following the procedure **6b** and purified by column chromatography using EtOAc/hexane and isolated as a yellow liquid. The ee was determined by chiral-phase HPLC using a Daicel Chiralcel OD-H column (hexane/*i*-PrOH = 90:10, flow rate 0.5 mL/min, λ = 254 nm), t_R = 38.0 min (major), t_R = 52.2 min (minor), t_R



133sa/134sa
dr = 1:1.6

= 59.8 min (major), t_R = 64.8 min (minor); **$[\alpha]^{25}_D$ = –6.7 (*c* 0.3, $CHCl_3$, 61% ee, 11% ee)**; IR (neat): ν_{max} 3028, 2955, 1732 (O-C=O), 1668 (C=O), 1553, 1497, 1435, 1377, 1204, 1161 and 700 cm^{-1}; ^1H NMR ($CDCl_3$, 1:1.6 ratio of diastereomers) δ 7.32-7.28 (4H, m), 7.25-7.21 (6H, m), 5.29 (1H, dd, *J* = 12.4, 9.2 Hz), 5.24-5.12 (2H, m), 5.07 (1H, dd, *J* = 12.4, 6.0 Hz), 4.85-4.77 (2H, m), 3.77 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 3.40 (1H, t, *J* = 4.4 Hz), 3.37 (1H, t, *J* = 4.8 Hz), 2.61-2.52 (1H, m), 2.50-2.41 (2H, m), 2.39-2.31 (1H, m), 2.30-2.19 (4H, m), 2.16 (3H, s, olefinic-CH_3), 2.12 (3H, s, olefinic-CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135, 1.6:1 ratio of diastereomers) δ 197.4 (C, C=O), 197.1 (C, C=O), 172.0 (C, O-C=O), 171.8 (C, O-C=O), 155.0 (C), 154.6 (C), 138.5 (C), 138.1 (C), 135.6 (C), 135.1 (C), 128.7 (4 x CH), 127.5 (CH), 127.2 (CH), 127.1 (4 x CH), 77.7 (CH_2), 77.6 (CH_2), 52.6 (CH_3, O*C*H_3), 52.5 (CH_3, O*C*H_3), 48.3 (CH), 48.2 (CH), 42.2 (CH), 42.0 (CH), 35.4 (CH_2), 35.3 (CH_2), 25.2 (CH_2), 25.1 (CH_2), 21.3 (CH_3, olefinic-*C*H_3), 21.1 (CH_3, olefinic-*C*H_3); LRMS m/z 318.00 ($M + H^+$), calcd $C_{17}H_{19}NO_5$ 317.1263; Anal. calcd for $C_{17}H_{19}NO_5$ (317.12): C, 64.34; H, 6.03; N, 4.41. Found: C, 64.41; H, 6.08; N, 4.45%.

(*S*,*S*)-2-Methyl-3-(2-nitro-1-phenylethyl)-4-oxo-cyclohex-2-enecarboxylic acid *tert*-butyl ester (133ba) and (*S*,*R*)-2-Methyl-3-(2-nitro-1-phenylethyl)-4-oxo-cyclohex-2-enecarboxylic acid *tert*-butyl ester (134ba): Prepared following the procedure **6b** and purified by column chromatography using EtOAc/hexane and isolated as a yellow liquid. The ee was determined by chiral-phase HPLC using a Daicel Chiralcel OD-H column (hexane/*i*-PrOH = 95:5, flow rate 0.5 mL/min, λ = 254 nm), t_R = 26.2 min (minor), t_R = 28.3 min (major), t_R = 37.0 min (major), t_R = 52.7 min (minor); **$[\alpha]^{25}_D$ = +31.0 (*c* 0.3, $CHCl_3$, 84% ee, 40% ee)**; IR (neat): ν_{max} 2978, 1724 (O-C=O), 1668 (C=O), 1553, 1372, 1254, 1148 and 698 cm^{-1}; ^1H NMR ($CDCl_3$, 2.1:1 ratio of diastereomers) δ 7.28 (4H, t, *J* = 7.2 Hz), 7.24-7.21 (6H, m), 5.30-5.21 (2H, m), 5.15-5.06 (2H, m), 4.84 (1H, t, *J* = 7.6 Hz), 4.76 (1H, dd, *J* = 8.8, 6.0 Hz), 3.27 (1H, t, *J* = 4.4 Hz), 3.24 (1H, t, *J* = 4.8 Hz), 2.62-2.45 (2H, m), 2.42-2.33 (2H, m), 2.31-2.20 (4H, m), 2.17 (3H, s, olefinic-



133ba/134ba
dr = 2.1:1

CH_3), 2.12 (3H, s, olefinic-CH_3), 1.48 (9H, s, 3 x CH_3, O-C(CH_3)$_3$), 1.41 (9H, s, 3 x CH_3, O-C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135, 2.1:1 ratio of diastereomers) δ 197.6 (C, C=O), 197.3 (C, C=O), 170.44 (C, O-C=O), 170.37 (C, O-C=O), 155.7 (C), 155.4 (C), 138.6 (C), 138.3 (C), 134.8 (C), 134.5 (C), 128.64 (2 x CH), 128.57 (2 x CH), 127.5 (2 x CH), 127.1 (3 x CH), 127.0 (CH), 82.3 (C, O-*C*(CH_3)$_3$), 82.1 (C, O-*C*(CH_3)$_3$), 77.6 (CH_2), 77.4 (CH_2), 49.51 (CH), 49.46 (CH), 42.01 (CH), 41.97 (CH), 35.3 (CH_2), 35.2 (CH_2), 27.8 (6 x CH_3, O-C(*C*H_3)$_3$), 25.3 (CH_2), 25.1 (CH_2), 21.3 (CH_3, olefinic-*C*H_3), 21.2 (CH_3, olefinic-*C*H_3); LRMS m/z 360.00 (M + H^+), calcd $C_{20}H_{25}NO_5$ 359.1733; Anal. calcd for $C_{20}H_{25}NO_5$ (359.17): C, 66.83; H, 7.01; N, 3.90. Found: C, 66.75; H, 7.08; N, 3.98%.

(*R*,*S*)-2-Methyl-3-(2-nitro-1-phenylethyl)-4-oxo-cyclohex-2-enecarboxylic acid *tert*-butyl ester (133ba) and (*R*,*R*)-2-Methyl-3-(2-nitro-1-phenylethyl)-4-oxo-cyclohex-2-enecarboxylic acid *tert*-butyl ester (134ba): Prepared following the procedure **6c** and purified by column chromatography using EtOAc/hexane and isolated as a yellow liquid. The ee was determined by chiral-phase HPLC using a Daicel Chiralcel OD-H column (hexane/*i*-PrOH = 95:5, flow rate 0.5 mL/min, λ = 254 nm), t_R = 28.2 min (major), t_R = 31.3 min (minor), t_R = 43.4 min (minor), t_R = 63.3 min (major); **$[\alpha]^{25}_D$ = –32.4 (*c* 0.3, $CHCl_3$, –85% ee, –8% ee)**; IR (neat): ν_{max} 2978, 1724 (O-C=O), 1668 (C=O), 1553, 1372, 1254, 1148 and 698 cm^{-1}.

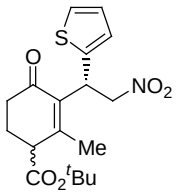
(–)-**133ba/134ba**
dr = 1:1

(*S*,*S*)-3-[1-(2-Chlorophenyl)-2-nitro-ethyl]-2-methyl-4-oxo-cyclohex-2-enecarboxylic acid *tert*-butyl ester (133bc) and (*S*,*R*)-3-[1-(2-Chlorophenyl)-2-nitro-ethyl]-2-methyl-4-oxo-cyclohex-2-enecarboxylic acid *tert*-butyl ester (134bc): Prepared following the procedure **6b** and purified by column chromatography using EtOAc/hexane and isolated as a yellow liquid. The ee was determined by chiral-phase HPLC using a Daicel Chiralcel OD-H column (hexane/*i*-PrOH = 90:10, flow rate 1.0 mL/min, λ = 254

133bc/134bc
dr = 1.5:1

nm), t_R = 7.6 min (minor), t_R = 8.6 min (major), t_R = 12.2 min (major), t_R = 14.4 min (minor); **$[\alpha]^{25}_D$ = +21.4 (*c* 0.15, $CHCl_3$, 83% ee, 33% ee)**; IR (neat): ν_{max} 2976, 2932, 1726 (O-C=O), 1668 (C=O), 1555, 1372, 1258, 1150, 845 and 758 cm^{-1}; ^1H NMR ($CDCl_3$, 1.5:1 ratio of diastereomers) δ 7.48 (1H, dd, *J* = 7.6, 1.6 Hz), 7.38-7.33 (3H, m), 7.24-7.18 (4H, m), 5.41 (1H, dd, *J* = 12.8, 9.6 Hz), 5.27 (1H, dd, *J* = 12.4, 8.4 Hz), 5.10 (1H, dd, *J* = 8.4, 6.4 Hz), 5.05-4.98 (2H, m), 4.83 (1H, dd, *J* = 13.2, 5.6 Hz), 3.26-3.22 (2H, m), 2.64-2.52 (2H, m), 2.43 (1H, td, *J* = 17.2, 4.8 Hz), 2.35-2.20 (4H, m), 2.17 (3H, s, olefinic-CH_3), 2.02 (3H, s, olefinic-CH_3), 1.48 (9H, s, 3 x CH_3, O-C(CH_3)$_3$), 1.38 (9H, s, 3 x CH_3, O-C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135, 1.5:1 ratio of diastereomers) δ 198.4 (C, C=O), 198.1 (C, C=O), 170.4 (C, O-C=O), 170.3 (C, O-C=O), 157.0 (C), 156.9 (C), 135.34 (C), 135.30 (C), 133.6 (C), 133.4 (C), 133.2 (C), 132.8 (C), 130.3 (CH), 130.1 (CH), 129.7 (CH), 129.6 (CH), 128.7 (CH), 128.6 (CH), 127.2 (CH), 127.1 (CH), 82.4 (C, O-*C*(CH_3)$_3$), 82.0 (C, O-*C*(CH_3)$_3$), 76.0 (CH_2), 75.7 (CH_2), 49.6 (2 x CH), 40.3 (CH), 39.9 (CH), 35.34 (CH_2), 35.26 (CH_2), 27.9 (3 x CH_3, O-C(*C*H_3)$_3$), 27.8 (3 x CH_3, O-C(*C*H_3)$_3$), 25.2 (CH_2), 25.0 (CH_2), 21.6 (CH_3, olefinic-*C*H_3), 21.2 (CH_3, olefinic-*C*H_3); LRMS m/z 394.00 (M + H^+), calcd $C_{20}H_{24}ClNO_5$ 393.1343; Anal. calcd for $C_{20}H_{24}ClNO_5$ (393.13): C, 60.99; H, 6.14; N, 3.56. Found: C, 61.05; H, 6.10; N, 3.61%.

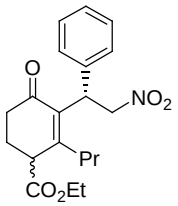
(*S*,*S*)-2-Methyl-3-(2-nitro-1-thiophen-2-yl-ethyl)-4-oxo-cyclohex-2-enecarboxylic acid *tert*-butyl ester (133bd) and (*S*,*R*)-2-Methyl-3-(2-nitro-1-thiophen-2-yl-ethyl)-4-oxo-cyclohex-2-enecarboxylic acid *tert*-butyl ester (134bd): Prepared following the procedure **6b** and purified by column chromatography using EtOAc/hexane and isolated as a yellow liquid. The ee was determined by chiral-phase HPLC using a Daicel Chiralpak AS-H column (hexane/*i*-PrOH = 90:10, flow rate 0.5 mL/min, λ = 254 nm), t_R = 14.8 min (major), t_R = 17.8 min (minor), t_R = 19.3 min (major), t_R = 22.3 min (minor); **$[\alpha]^{25}_D$ = +43.1 (*c* 0.2, $CHCl_3$, 69% ee, 11% ee)**; IR (neat): ν_{max} 2978, 2930, 1722 (O-C=O), 1667 (C=O), 1555, 1370, 1260, 1150 and 845 cm^{-1}; ^1H NMR



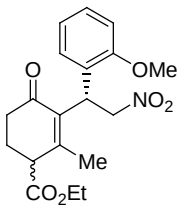
133bd/134bd
dr = 5.2:1

($CDCl_3$, 5.2:1 ratio of diastereomers, major isomer) δ 7.16 (1H, t, *J* = 3.2 Hz), 6.92 (2H, d, *J* = 3.2 Hz), 5.26-5.20 (1H, m), 5.11-5.05 (2H, m), 3.25 (1H, t, *J* = 4.8 Hz), 2.64-2.55 (1H, m), 2.37 (1H, td, *J* = 17.2, 4.8 Hz), 2.29-2.22 (1H, m), 2.18 (3H, s, olefinic-CH_3), 2.18-2.11 (1H, m), 1.48 (9H, s, 3 x CH_3, O-C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135, 5.2:1 ratio of diastereomers, major isomer) δ 197.3 (C, C=O), 170.3 (C, O-C=O), 155.7 (C), 141.0 (C), 134.3 (C), 126.8 (CH), 125.4 (CH), 124.8 (CH), 82.4 (C, O-*C*$(CH_3)_3$), 78.0 (CH_2), 49.6 (CH), 38.3 (CH), 35.3 (CH_2), 27.9 (3 x CH_3, O-C(*C*H_3)$_3$), 25.2 (CH_2), 21.1 (CH_3, olefinic-*C*H_3); LRMS m/z 364.00 (M – H^+), calcd $C_{18}H_{23}NO_5S$ 365.1297; Anal. calcd for $C_{18}H_{23}NO_5S$ (365.12): C, 59.16; H, 6.34; N, 3.83. Found: C, 59.32; H, 6.25; N, 3.92%.

(*S*,*S*)-3-(2-Nitro-1-phenylethyl)-4-oxo-2-propyl-cyclohex-2-enecarboxylic acid ethyl ester (133ha) and (*S*,*R*)-3-(2-Nitro-1-phenylethyl)-4-oxo-2-propyl-cyclohex-2-enecarboxylic acid ethyl ester (134ha): Prepared following the procedure **6b** and purified by column chromatography using EtOAc/hexane and isolated as a yellow liquid. The ee was determined by chiral-phase HPLC using a Daicel Chiralcel AD-H column (hexane/*i*-PrOH = 95:5, flow rate 0.5 mL/min, λ = 254 nm), t_R = 20.6 min (minor), t_R = 23.5 min (major), t_R = 28.9 min (major), t_R = 49.2 min (minor); **$[\alpha]^{25}_D$ = +7.3 (*c* 0.25, $CHCl_3$, 77% ee, 3% ee)**; IR (neat): ν_{max} 2964, 1728 (O-C=O), 1669 (C=O), 1551, 1375, 1188 and 1158 cm^{-1}; ^{1}H NMR ($CDCl_3$, 2:1 ratio of diastereomers) δ 7.32-7.28 (4H, m), 7.25-7.20 (6H, m), 5.30-5.05 (4H, m), 4.86 (1H, t, *J* = 7.2 Hz), 4.79-4.72 (1H, m), 4.21 (2H, q, *J* = 7.2 Hz, OC$H_2$$CH_3$), 4.18 (2H, q, *J* = 7.2 Hz, OC$H_2$$CH_3$), 3.48-3.43 (2H, m), 2.66-2.44 (4H, m), 2.42-2.25 (3H, m), 2.24-2.08 (4H, m), 1.55-1.35 (5H, m), 1.29 (3H, t, *J* = 7.2 Hz, OCH_2CH_3), 1.24 (3H, t, *J* = 7.2 Hz, OCH_2CH_3), 0.98 (6H, t, *J* = 7.2 Hz, 2 x CH_2CH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135, 2:1 ratio of diastereomers) δ 197.8 (C, C=O), 197.6 (C, C=O), 171.5 (C, O-C=O), 171.4 (C, O-C=O), 159.0 (C), 158.8 (C), 138.8 (C), 138.5 (C), 135.1 (C), 134.8 (C), 128.6 (4 x CH),



133ha/134ha
dr = 2.0:1

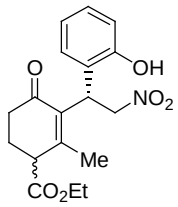


133ae/134ae
dr = 1.2:1

127.3 (2 x CH), 127.0 (4 x CH), 78.1 (2 x CH_2), 61.6 (CH_2, O*C*H_2CH_3), 61.5 (CH_2, OCH_2*C*H_3), 46.2 (CH), 45.8 (CH), 41.9 (2 x CH), 36.7 (CH_2), 36.5 (CH_2), 35.0 (2 x CH_2), 25.5 (CH_2), 25.4 (CH_2), 21.3 (2 x CH_2), 14.4 (2 x CH_3, OCH$_2$*C*H_3), 14.10 (CH_3, CH_2CH_2*C*H_3), 14.07 (CH_3, CH_2CH_2*C*H_3); LRMS m/z 360.00 (M + H^+), calcd $C_{20}H_{25}NO_5$ 359.1733; Anal. calcd for $C_{20}H_{25}NO_5$ (359.17): C, 66.83; H, 7.01; N, 3.90. Found: C, 66.75; H, 7.05; N, 3.96%.

(*S*,*S*)-3-[1-(2-Methoxyphenyl)-2-nitroethyl]-2-methyl-4-oxo-cyclohex-2-enecarboxylic acid ethyl ester (133ae) and (*S*,*R*)-3-[1-(2-Methoxyphenyl)-2-nitroethyl]-2-methyl-4-oxo-cyclohex-2-enecarboxylic acid ethyl ester (134ae): Prepared following the procedure **6b** and purified by column chromatography using EtOAc/hexane and isolated as a yellow liquid. The ee was determined by chiral-phase HPLC using a Daicel Chiralcel OD-H column (hexane/*i*-PrOH = 95:5, flow rate 1.0 mL/min, λ = 254 nm), t_R = 17.5 min (major), t_R = 19.0 min (minor), t_R = 23.8 min (minor), t_R = 26.6 min (major); **$[\alpha]^{25}_D$ = +26.0 (*c* 0.3, $CHCl_3$, 78% ee, 17% ee)**; IR (neat): ν_{max} 2979, 1728 (O-C=O), 1665 (C=O), 1550, 1492, 1375, 1246, 1160 and 1028 cm^{-1}; ^{1}H NMR ($CDCl_3$, 1.2:1 ratio of diastereomers) δ 7.31 (1H, d, *J* = 7.6 Hz), 7.23-7.18 (3H, m), 6.91-6.84 (4H, m), 5.34-5.22 (2H, m), 5.16 (1H, dd, *J* = 8.4, 6.0 Hz), 5.05-5.00 (2H, m), 4.90 (1H, dd, *J* = 12.8, 5.2 Hz), 4.20 (2H, q, *J* = 7.2 Hz, OCH_2CH$_3$), 4.15 (2H, q, *J* = 7.2 Hz, OCH_2CH$_3$), 3.83 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.35 (1H, t, *J* = 4.8 Hz), 3.32 (1H, t, *J* = 4.4 Hz), 2.60-2.51 (2H, m), 2.43-2.28 (2H, m), 2.26-2.20 (3H, m), 2.15 (3H, s, olefinic-CH_3), 2.12-2.07 (1H, m), 2.03 (3H, s, olefinic-CH_3), 1.29 (3H, t, *J* = 7.2 Hz, OCH$_2$CH_3), 1.22 (3H, t, *J* = 7.2 Hz, OCH$_2$CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135, 1.2:1 ratio of diastereomers) δ 197.74 (C, C=O), 197.66 (C, C=O), 171.4 (C, O-C=O), 171.3 (C, O-C=O), 156.54 (C), 156.47 (C), 155.32 (C), 155.26 (C), 134.1 (C), 133.9 (C), 129.0 (CH), 128.9 (CH), 128.23 (CH), 128.17 (CH), 126.0 (C), 125.7 (C), 120.4 (2 x CH), 110.2 (CH), 110.0 (CH), 76.8 (CH_2), 76.6 (CH_2), 61.3 (CH_2, O*C*H_2CH_3), 61.1 (CH_2, O*C*H_2CH_3), 55.2 (CH_3, O*C*H_3), 55.1 (CH_3, O*C*H_3), 48.4 (CH), 48.2 (CH), 36.8 (CH), 36.2 (CH), 35.3 (CH_2), 35.2 (CH_2), 25.1

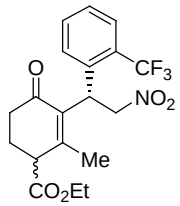
(CH_2), 24.9 (CH_2), 21.1 (CH_3, olefinic-*C*H_3), 20.7 (CH_3, olefinic-*C*H_3), 14.0 (CH_3, OCH_2*C*H_3), 13.9 (CH_3, OCH_2*C*H_3); LRMS m/z 360.25 ($M - H^+$), calcd $C_{19}H_{23}NO_6$ 361.1525; Anal. calcd for $C_{19}H_{23}NO_6$ (361.15): C, 63.15; H, 6.41; N, 3.88. Found: C, 63.09; H, 6.45; N, 3.95%.



133af/134af
dr = 1.2:1

(*S*,*S*)-3-[1-(2-Hydroxyphenyl)-2-nitroethyl]-2-methyl-4-oxo-cyclohex-2-enecarboxylic acid ethyl ester (133af) and (*S*,*R*)-3-[1-(2-Hydroxyphenyl)-2-nitroethyl]-2-methyl-4-oxo-cyclohex-2-enecarboxylic acid ethyl ester (134af): Prepared following the procedure **6b** and purified by column chromatography using EtOAc/hexane and isolated as a dark yellow liquid. The ee was determined by chiral-phase HPLC using a Daicel Chiralpak AS-H column (hexane/*i*-PrOH = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 16.0 min (major), t_R = 17.6 min (minor), t_R = 34.4 min (minor), t_R = 44.9 min (major); **$[\alpha]^{25}_D$ = –10.7 (*c* 0.3, $CHCl_3$, 26% ee, 21% ee)**; IR (neat): ν_{max} 3360 (O-*H*), 2928, 1730 (O-C=O), 1661 (C=O), 1553, 1456, 1375 and 756 cm^{-1}; ^1H NMR ($CDCl_3$, 1.2:1 ratio of diastereomers) δ 7.24 (1H, d, *J* = 7.6 Hz), 7.17-7.13 (2H, m), 7.09 (3H, t, *J* = 7.6 Hz), 6.86-6.81 (2H, m), 6.78 (2H, m), 5.34 (1H, dd, *J* = 12.0, 9.2 Hz), 5.27 (1H, dd, *J* = 12.4, 8.8 Hz), 5.12 (1H, dd, *J* = 8.8, 6.0 Hz), 5.07-5.02 (2H, m), 4.98 (1H, dd, *J* = 16.4, 4.4 Hz), 4.21 (2H, q, *J* = 7.2 Hz, OCH_2CH_3), 4.15 (2H, q, *J* = 7.2 Hz, OCH_2CH_3), 3.38 (1H, t, *J* = 4.4 Hz), 3.34 (1H, t, *J* = 4.4 Hz), 2.65-2.54 (2H, m), 2.46 (1H, td, *J* = 17.2, 4.8 Hz), 2.38 (1H, td, *J* = 17.2, 4.8 Hz), 2.26-2.23 (3H, m), 2.20 (3H, s, olefinic-CH_3), 2.18-2.13 (1H, m), 2.10 (3H, s, olefinic-CH_3), 1.29 (3H, t, *J* = 7.2 Hz, OCH_2CH_3), 1.22 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135, 1.2:1 ratio of diastereomers) δ 199.3 (C, C=O), 199.2 (C, C=O), 171.6 (C, O-C=O), 171.5 (C, O-C=O), 156.9 (C), 156.8 (C), 153.8 (C), 153.7 (C), 134.3 (C), 134.1 (C), 129.4 (2 x CH), 128.44 (CH), 128.38 (CH), 124.1 (C), 123.9 (C), 120.4 (CH), 120.3 (CH), 115.9 (2 x CH), 76.6 (CH_2), 76.3 (CH_2), 61.6 (CH_2, O*C*H_2CH_3), 61.5 (CH_2, O*C*H_2CH_3), 48.5 (CH), 48.4 (CH), 37.6 (CH), 37.0 (CH), 35.14 (CH_2), 35.07 (CH_2), 25.0 (CH_2), 24.8 (CH_2), 21.4 (CH_3, olefinic-*C*H_3), 21.1

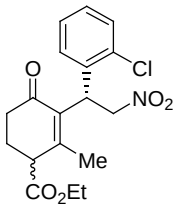
(CH_3, olefinic-*C*H_3), 13.9 (2 x CH_3, OCH_2*C*H_3); LRMS m/z 346.20 ($M - H^+$), calcd $C_{18}H_{21}NO_6$ 347.1369; Anal. calcd for $C_{18}H_{21}NO_6$ (347.13): C, 62.24; H, 6.09; N, 4.03. Found: C, 62.41; H, 6.15; N, 4.10%.



133ag/134ag
dr = 1:1.4

(*S*,*S*)-2-Methyl-3-[2-nitro-1-(2-trifluoromethylphenyl)ethyl]-4-oxo-cyclohex-2-enecarboxylic acid ethyl ester (133ag) and (*S*,*R*)-2-Methyl-3-[2-nitro-1-(2-trifluoromethylphenyl)ethyl]-4-oxo-cyclohex-2-enecarboxylic acid ethyl ester (134ag): Prepared following the procedure **6b** and purified by column chromatography using EtOAc/hexane and isolated as a yellow liquid. The ee was determined by chiral-phase HPLC using a Daicel Chiralpak AD-H column (hexane/*i*-PrOH = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 6.0 min (major), t_R = 6.7 min (minor), t_R = 7.2 min (major), t_R = 12.6 min (minor); **$[\alpha]^{25}_D$ = +5.7 (*c* 0.3, $CHCl_3$, 44% ee, 15% ee)**; IR (neat): ν_{max} 1729 (O-C=O), 1667 (C=O), 1553, 1376, 1309, 1160, 1118, 1038 and 771 cm^{-1}; ^{1}H NMR ($CDCl_3$, 1:1.4 ratio of diastereomers) δ 7.72 (1H, d, *J* = 8.0 Hz), 7.67 (2H, t, *J* = 8.4 Hz), 7.58 (1H, d, *J* = 8.0 Hz), 7.51 (2H, m), 7.38 (2H, m), 5.61 (1H, dd, *J* = 13.2, 10.8 Hz), 5.34 (1H, dd, *J* = 12.8, 8.4 Hz), 5.19 (1H, t, *J* = 7.2 Hz), 5.04-4.97 (2H, m), 4.71 (1H, dd, *J* = 13.6, 4.8 Hz), 4.21 (2H, q, *J* = 7.2 Hz, OC*H*$_2$$CH_3$), 4.13 (2H, q, *J* = 7.2 Hz, OC*H*$_2$$CH_3$), 3.37 (1H, t, *J* = 4.4 Hz), 3.33 (1H, t, *J* = 4.8 Hz), 2.65-2.45 (3H, m), 2.34 (1H, td, *J* = 17.2, 3.6 Hz), 2.27-2.24 (3H, m), 2.17-2.07 (1H, m), 2.11 (3H, s, olefinic-C*H*$_3$), 1.95 (3H, s, olefinic-C*H*$_3$), 1.30 (3H, t, *J* = 7.2 Hz, OCH_2C*H*$_3$), 1.19 (3H, t, *J* = 7.2 Hz, OCH_2C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135, 1:1.4 ratio of diastereomers) δ 198.8 (C, C=O), 198.3 (C, C=O), 171.2 (C, O-C=O), 171.1 (C, O-C=O), 156.41 (C), 156.38 (C), 136.4 (C), 136.1 (C), 134.3 (C), 134.2 (C), 132.5 (CH), 132.1 (CH), 131.3 (CH), 131.0 (CH), 128.3 (CF_3, q, *J* = 30.0 Hz), 128.1 (CF_3, q, *J* = 30.0 Hz), 127.7 (CH), 127.5 (CH), 126.54 (CH, q, *J* = 6.0 Hz), 126.51 (CH, q, *J* = 6.0 Hz), 125.8 (C, d, *J* = 4.0 Hz), 123.1 (C, d, *J* = 3.0 Hz), 76.3 (CH_2), 76.0 (CH_2), 61.6 (CH_2, O*C*H_2CH_3), 61.4 (CH_2, O*C*H_2CH_3), 48.7 (CH), 48.6 (CH), 39.8 (CH), 39.1 (CH), 35.4 (CH_2), 35.3 (CH_2), 24.9 (CH_2), 24.6 (CH_2), 21.3 (CH_3, olefinic-*C*H_3), 20.9

(CH_3, olefinic-*C*H_3), 14.01 (CH_3, OCH_2CH_3), 13.98 (CH_3, OCH_2CH_3); LRMS m/z 400.00 ($M + H^+$), calcd $C_{19}H_{20}F_3NO_5$ 399.1294; Anal. calcd for $C_{19}H_{20}F_3NO_5$ (399.12): C, 57.14; H, 5.05; N, 3.51. Found: C, 57.08; H, 5.09; N, 3.58%.

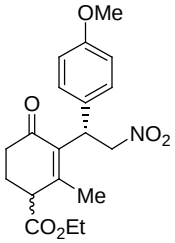


133ac/134ac
dr = 1.1:1

(*S*,*S*)-3-[1-(2-Chlorophenyl)-2-nitroethyl]-2-methyl-4-oxo-cyclohex-2-enecarboxylic acid ethyl ester (133ac) and (*S*,*R*)-3-[1-(2-Chlorophenyl)-2-nitroethyl]-2-methyl-4-oxo-cyclohex-2-enecarboxylic acid ethyl ester (134ac): Prepared following the procedure **6b** and purified by column chromatography using EtOAc/hexane and isolated as a yellow liquid. The ee was determined by chiral-phase HPLC using a Daicel Chiralcel OD-H column (hexane/*i*-PrOH = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 11.2 min (minor), t_R = 12.9 min (major), t_R = 14.9 min (major), t_R = 19.0 min (minor); **$[\alpha]^{25}_D$ = +5.3 (*c* 0.3, $CHCl_3$, 60% ee, 4% ee)**; IR (neat): ν_{max} 1728 (O-C=O), 1667 (C=O), 1552, 1442, 1375, 1158 and 1018 cm^{-1}; ^1H NMR ($CDCl_3$, 1.1:1 ratio of diastereomers) δ 7.49 (1H, dd, *J* = 8.0, 1.6 Hz), 7.38-7.33 (3H, m), 7.25-7.17 (4H, m), 5.40 (1H, dd, *J* = 12.8, 3.2 Hz), 5.24 (1H, dd, *J* = 12.0, 4.0 Hz), 5.11 (1H, t, *J* = 6.4 Hz), 5.07-5.02 (2H, m), 4.85 (1H, dd, *J* = 12.8, 5.2 Hz), 4.21 (2H, q, *J* = 7.2 Hz, OCH_2CH_3), 4.15 (2H, q, *J* = 7.2 Hz, OCH_2CH_3), 3.36-3.34 (2H, m), 2.62-2.51 (2H, m), 2.47-2.41 (1H, m), 2.35-2.21 (4H, m), 2.18 (3H, s, olefinic-CH_3), 2.16-2.08 (1H, m), 2.02 (3H, s, olefinic-CH_3), 1.29 (3H, t, *J* = 7.2 Hz, OCH_2CH_3), 1.21 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135, 1.1:1 ratio of diastereomers) δ 198.1 (C, C=O), 197.7 (C, C=O), 171.2 (C, O-C=O), 171.1 (C, O-C=O), 156.3 (C), 156.2 (C), 135.2 (C), 135.1 (C), 133.6 (C), 133.5 (C), 133.4 (C), 133.1 (C), 130.2 (CH), 130.0 (CH), 129.7 (CH), 129.6 (CH), 128.7 (CH), 128.6 (CH), 127.2 (CH), 127.0 (CH), 76.1 (CH_2), 75.7 (CH_2), 61.6 (CH_2, OCH_2CH_3), 61.4 (CH_2, OCH_2CH_3), 48.42 (CH), 48.39 (CH), 40.2 (CH), 39.9 (CH), 35.3 (CH_2), 35.2 (CH_2), 25.1 (CH_2), 24.9 (CH_2), 21.6 (CH_3, olefinic-CH_3), 21.2 (CH_3, olefinic-CH_3), 14.04 (CH_3, OCH_2CH_3), 14.02 (CH_3, OCH_2CH_3); LRMS m/z 365.00 (M^+), calcd

$C_{18}H_{20}ClNO_5$ 365.1030; Anal. calcd for $C_{18}H_{20}ClNO_5$ (365.10): C, 59.10; H, 5.51; N, 3.83. Found: C, 59.15; H, 5.54; N, 3.88%.

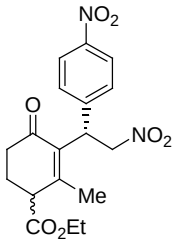
(*S*,*S*)-3-[1-(4-Methoxyphenyl)-2-nitroethyl]-2-methyl-4-oxo-cyclohex-2-enecarboxylic acid ethyl ester (133ah) and (*S*,*R*)-3-[1-(4-Methoxyphenyl)-2-nitroethyl]-2-methyl-4-oxo-cyclohex-2-enecarboxylic acid ethyl ester (134ah): Prepared following the procedure **6b** and purified by column chromatography using EtOAc/hexane and isolated as a yellow liquid. The ee was determined by chiral-phase HPLC using a Daicel Chiralpak AD-H column (hexane/*i*-PrOH = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 10.3 min (minor), t_R = 11.1 min (major), t_R = 17.1 min (major), t_R = 20.8 min (minor); **$[\alpha]^{25}_D$ = +8.3 (*c* 0.3, $CHCl_3$, 29% ee, 27% ee)**; IR (neat): ν_{max} 2926, 2856, 1727 (O-C=O), 1666 (C=O), 1550, 1513, 1376, 1250, 1183 and 1034 cm^{-1}; ^1H NMR ($CDCl_3$, 1:1.7 ratio of diastereomers) δ 7.18 (2H, d, *J* = 8.8 Hz), 7.15 (2H, d, *J* = 8.8 Hz), 6.82 (4H, d, *J* = 8.4 Hz), 5.25 (1H, dd, *J* = 12.4, 9.2 Hz), 5.14 (2H, d, *J* = 7.2 Hz), 5.03 (1H, dd, *J* = 12.8, 6.4 Hz), 4.77 (1H, t, *J* = 7.6 Hz), 4.71 (1H, dd, *J* = 8.8, 6.4 Hz), 4.21 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 4.18 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 3.76 (6H, s, 2 x OC*H*$_3$), 3.36 (1H, t, *J* = 4.4 Hz), 3.33 (1H, t, *J* = 4.4 Hz), 2.61-2.51 (1H, m), 2.46 (1H, dd, *J* = 12.0, 5.6 Hz), 2.41 (1H, t, *J* = 4.8 Hz), 2.35 (1H, t, *J* = 4.0 Hz), 2.32-2.17 (4H, m), 2.15 (3H, s, olefinic-C*H*$_3$), 2.11 (3H, s, olefinic-C*H*$_3$), 1.29 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$), 1.24 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135, 1:1.7 ratio of diastereomers) δ 197.5 (C, C=O), 197.2 (C, C=O), 171.4 (C, O-C=O), 171.3 (C, O-C=O), 158.5 (C), 158.4 (C), 154.8 (C), 154.4 (C), 135.4 (C), 135.0 (C), 130.4 (C), 130.1 (C), 128.6 (2 x CH), 128.2 (2 x CH), 113.9 (4 x CH), 77.8 (2 x CH_2), 61.5 (CH_2, O*C*H$_2$CH$_3$), 61.3 (CH_2, O*C*H$_2$CH$_3$), 55.1 (2 x CH_3, O*C*H$_3$), 48.3 (CH), 48.2 (CH), 41.5 (CH), 41.3 (CH), 35.3 (CH_2), 35.2 (CH_2), 25.2 (CH_2), 25.0 (CH_2), 21.1 (CH_3, olefinic-*C*H$_3$), 21.0 (CH_3, olefinic-*C*H$_3$), 14.0 (2 x CH_3, OCH$_2$*C*H$_3$); LRMS m/z



133ah/134ah
dr = 1:1.7

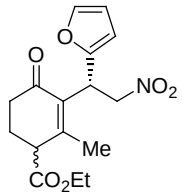
360.20 (M – H^+), calcd $C_{19}H_{23}NO_6$ 361.1525; Anal. calcd for $C_{19}H_{23}NO_6$ (361.15): C, 63.15; H, 6.41; N, 3.88. Found: C, 63.21; H, 6.45; N, 3.84%.

(*S*,*S*)-2-Methyl-3-[2-nitro-1-(4-nitrophenyl)ethyl]-4-oxo-cyclohex-2-enecarboxylic acid ethyl ester (133ai) and (*S*,*R*)-2-Methyl-3-[2-nitro-1-(4-nitrophenyl)ethyl]-4-oxo-cyclohex-2-enecarboxylic acid ethyl ester (134ai): Prepared following the procedure **6b** and purified by column chromatography using EtOAc/hexane and isolated as a yellow liquid. The ee was determined by chiral-phase HPLC using a Daicel Chiralpak AD-H column (hexane/*i*-PrOH = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 19.2 min (major), t_R = 25.2 min (major), t_R = 41.1 min (minor), t_R = 66.9 min (minor); **$[\alpha]^{25}_D$ = –48.7 (*c* 0.3, $CHCl_3$, 42% ee, 27% ee)**; IR (neat): ν_{max} 2958, 1727 (O-C=O), 1667 (C=O), 1552, 1520, 1346, 1160, 853 and 670 cm^{-1}; ^1H NMR ($CDCl_3$, 1:1.7 ratio of diastereomers) δ 8.15 (2H, d, *J* = 8.4 Hz), 8.14 (2H, d, *J* = 8.4 Hz), 7.44 (2H, d, *J* = 8.8 Hz), 7.42 (2H, d, *J* = 8.4 Hz), 5.30 (1H, dd, *J* = 13.2, 5.6 Hz), 5.20 (2H, dd, *J* = 6.8, 3.6 Hz), 5.08 (1H, dd, *J* = 13.2, 7.2 Hz), 4.96 (1H, t, *J* = 7.2 Hz), 4.88 (1H, t, *J* = 7.2 Hz), 4.24 (2H, q, *J* = 7.2 Hz, OCH_2CH_3), 4.22 (2H, q, *J* = 7.2 Hz, OCH_2CH_3), 3.44 (1H, t, *J* = 4.4 Hz), 3.41 (1H, t, *J* = 4.8 Hz), 2.63-2.53 (1H, m), 2.43 (2H, dd, *J* = 11.2, 5.6 Hz), 2.36 (1H, t, *J* = 4.8 Hz), 2.32-2.26 (3H, m), 2.22 (3H, s, olefinic-CH_3), 2.19 (3H, s, olefinic-CH_3), 2.17-2.12 (1H, m), 1.31 (3H, t, *J* = 7.2 Hz, OCH_2CH_3), 1.28 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135, 1:1.7 ratio of diastereomers) δ 197.1 (C, C=O), 196.7 (C, C=O), 171.1 (C, O-C=O), 170.9 (C, O-C=O), 156.5 (C), 156.1 (C), 146.8 (C), 146.7 (C), 146.0 (C), 145.9 (C), 134.6 (C), 134.3 (C), 128.3 (2 x CH), 127.8 (2 x CH), 123.7 (4 x CH), 76.8 (CH_2), 76.6 (CH_2), 61.7 (CH_2, OCH_2CH_3), 61.6 (CH_2, OCH_2CH_3), 48.24 (CH), 48.16 (CH), 41.6 (CH), 41.5 (CH), 35.0 (CH_2), 34.9 (CH_2), 25.1 (CH_2), 25.0 (CH_2), 21.4 (CH_3, olefinic-CH_3), 21.3 (CH_3, olefinic-CH_3), 14.1 (CH_3, OCH_2CH_3), 14.0 (CH_3, OCH_2CH_3); LRMS m/z 377.25 (M + H^+), calcd $C_{18}H_{20}N_2O_7$ 376.1271; Anal. calcd for $C_{18}H_{20}N_2O_7$ (376.12): C, 57.44; H, 5.36; N, 7.44. Found: C, 57.36; H, 5.39; N, 7.56%.



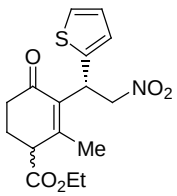
133ai/134ai
dr = 1:1.7

(*S*,*S*)-3-(1-Furan-2-yl-2-nitroethyl)-2-methyl-4-oxo-cyclohex-2-enecarboxylic acid ethyl ester (133aj) and (*S*,*R*)-3-(1-Furan-2-yl-2-nitroethyl)-2-methyl-4-oxo-cyclohex-2-enecarboxylic acid ethyl ester (134aj): Prepared following the procedure **6b** and purified by column chromatography using EtOAc/hexane and isolated as a yellow liquid. The ee was determined by chiral-phase HPLC using a Daicel Chiralpak AS-H column (hexane/*i*-PrOH = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 11.4 min (major), t_R = 12.3 min (major), t_R = 14.1 min (minor), t_R = 15.5 min (minor); **$[\alpha]^{25}_D$ = +10.7 (*c* 0.3, $CHCl_3$, 47% ee, 6% ee)**; IR (neat): ν_{max} 2983, 1728 (O-C=O), 1670 (C=O), 1553, 1375, 1256, 1189, 1020 and 801 cm^{-1}; ^1H NMR ($CDCl_3$, 1.1:1 ratio of diastereomers) δ 7.29 (2H, m), 6.29 (2H, m), 6.08 (2H, m), 5.19-5.11 (3H, m), 5.02-4.98 (2H, m), 4.92 (1H, t, *J* = 7.2 Hz), 4.22 (4H, q, *J* = 7.2 Hz, 2 x O*CH*$_2$CH$_3$), 3.38 (2H, t, *J* = 4.8 Hz, 2 x C*H*), 2.60-2.49 (2H, m), 2.44-2.34 (2H, m), 2.33-2.19 (4H, m), 2.16 (3H, s, olefinic-C*H*$_3$), 2.12 (3H, s, olefinic-C*H*$_3$), 1.29 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$), 1.28 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135, 1.1:1 ratio of diastereomers) δ 196.5 (C, C=O), 196.3 (C, C=O), 171.3 (C, O-C=O), 171.2 (C, O-C=O), 155.9 (C), 155.6 (C), 151.4 (C), 151.1 (C), 141.5 (CH), 141.4 (CH), 132.9 (C), 132.7 (C), 110.6 (2 x CH), 106.38 (CH), 106.37 (CH), 75.9 (CH_2), 75.8 (CH_2), 61.6 (CH_2, O*C*H$_2$CH$_3$), 61.5 (CH_2, O*C*H$_2$CH$_3$), 48.5 (CH), 48.3 (CH), 36.6 (CH), 36.3 (CH), 35.1 (CH_2), 34.9 (CH_2), 25.2 (2 x CH_2), 21.1 (CH_3, olefinic-*C*H$_3$), 20.8 (CH_3, olefinic-*C*H$_3$), 14.1 (CH_3, OCH$_2$*C*H$_3$), 14.0 (CH_3, OCH$_2$*C*H$_3$); LRMS m/z 322.15 (M + H^+), calcd $C_{16}H_{19}NO_6$ 321.1212; Anal. calcd for $C_{16}H_{19}NO_6$ (321.12): C, 59.81; H, 5.96; N, 4.36. Found: C, 59.88; H, 5.93; N, 4.42%.



133aj/134aj
dr = 1.1:1

(*S*,*S*)-2-Methyl-3-(2-nitro-1-thiophen-2-yl-ethyl)-4-oxo-cyclohex-2-enecarboxylic acid ethyl ester (133ad) and (*S*,*R*)-2-Methyl-3-(2-nitro-1-thiophen-2-yl-ethyl)-4-oxo-cyclohex-2-enecarboxylic acid ethyl ester (134ad): Prepared following the procedure **6b** and purified by column chromatography using EtOAc/hexane and isolated as a yellow liquid.



133ad/134ad
dr = 1.5:1

The ee was determined by chiral-phase HPLC using a Daicel Chiralpak AD-H column (hexane/*i*-PrOH = 98:2, flow rate 1.0 mL/min, λ = 254 nm), t_R = 22.8 min (major), t_R = 24.9 min (major), t_R = 26.7 min (minor), t_R = 43.0 min (minor); **$[\alpha]^{25}_D$ = +8.7 (*c* 0.3, $CHCl_3$, 41% ee, 12% ee)**; IR (neat): ν_{max} 2979, 1727 (O-C=O), 1667 (C=O), 1551, 1375, 1299, 1196, 1161 and 1039 cm^{-1}; ^1H NMR ($CDCl_3$, 1.5:1 ratio of diastereomers) δ 7.16 (1H, t, *J* = 1.6 Hz), 7.15 (1H, t, *J* = 2.0 Hz), 6.92 (2H, t, *J* = 2.0 Hz), 6.91-6.89 (2H, m), 5.28 (1H, dd, *J* = 12.4, 8.4 Hz), 5.16-5.13 (2H, m), 5.08 (2H, dd, *J* = 8.0, 2.0 Hz), 5.01 (1H, dd, *J* = 14.0, 4.8 Hz), 4.22 (2H, q, *J* = 6.8 Hz, OCH_2CH_3), 4.19 (2H, q, *J* = 7.2 Hz, OCH_2CH_3), 3.39-3.34 (2H, m), 2.63-2.49 (2H, m), 2.44-2.35 (2H, m), 2.32-2.20 (4H, m), 2.18 (3H, s, olefinic-CH_3), 2.15 (3H, s, olefinic-CH_3), 1.29 (3H, t, *J* = 7.2 Hz, OCH_2CH_3), 1.24 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135, 1.5:1 ratio of diastereomers) δ 197.0 (C, C=O), 196.7 (C, C=O), 171.2 (2 x C, O-C=O), 155.3 (C), 155.0 (C), 140.9 (C), 140.7 (C), 134.8 (C), 134.5 (C), 126.8 (2 x CH), 125.4 (CH), 125.0 (CH), 124.7 (CH), 124.5 (CH), 78.1 (CH_2), 77.9 (CH_2), 61.6 (CH_2, OCH_2CH_3), 61.5 (CH_2, OCH_2CH_3), 48.4 (CH), 48.2 (CH), 38.3 (CH), 38.2 (CH), 35.2 (CH_2), 35.0 (CH_2), 25.08 (CH_2), 25.06 (CH_2), 21.0 (CH_3, olefinic-CH_3), 20.8 (CH_3, olefinic-CH_3), 14.03 (CH_3, OCH_2CH_3), 14.01 (CH_3, OCH_2CH_3); LRMS m/z 338.00 ($M + H^+$), calcd $C_{16}H_{19}NO_5S$ 337.0984; Anal. calcd for $C_{16}H_{19}NO_5S$ (337.09): C, 56.96; H, 5.68; N, 4.15. Found: C, 56.88; H, 5.65; N, 4.19%.

7: Decarboxylation procedures:

7a: Synthesis of racemic 3-methyl-2-(2-nitro-1-phenylethyl)-cyclohex-2-enone (±)-142aa:

First step: In a 10 mL RB equipped with a magnetic stirring bar, to 0.3 mmol of 2-methyl-3-(2-nitro-1-phenylethyl)-4-oxo-cyclohex-2-enecarboxylic acid ethyl ester (±)-**133aa/134aa** was added mixture of MeOH (0.5 mL), H_2O (0.5 mL), THF (2 mL) as solvent and then $LiOH.H_2O$ (1.8 mmol, 6 equiv.) was added and the reaction mixture was stirred for 3 hours at RT as indicated in Scheme 22. The solvent was removed and washed with DCM (2 x 10 mL). The p*H* of the reaction mixture was adjusted to 2 with

2 mL of 1N aq. HCl furnished the ketoacid (±)-**140aa/141aa** which extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried with Na_2SO_4 and crude product proceeded for next step.

Second step: Ketoacid (±)-**140aa/141aa** (0.1 mmol) was dissolved in a mixture of concentrated HCl (0.1 mL) in THF (1.25 mL) and heated for 3h at 90 ºC in a sealed glass tube. The reaction mixture was concentrated and residue was partitioned between water and CH_2Cl_2. The combined organic layers were dried with Na_2SO_4 and concentrated. The residue was chromatographed to yield 3-methyl-2-(2-nitro-1-phenylethyl)-cyclohex-2-enone (±)-**142aa** as yellow oil.

7b: Synthesis of 3-methyl-2-(2-nitro-1-phenylethyl)-cyclohex-2-enone (*R*)-142aa:

First step: In a 10 mL RB equipped with a magnetic stirring bar, to 0.3 mmol of 2-methyl-3-(2-nitro-1-phenylethyl)-4-oxo-cyclohex-2-enecarboxylic acid ethyl ester (+)-**133aa/134aa** was added mixture of MeOH (0.5 mL), H_2O (0.5 mL), THF (2 mL) as a solvent and then $LiOH.H_2O$ (1.8 mmol, 6 equiv.) was added and the reaction mixture was stirred for 0.75 h at RT as indicated in Scheme 22. The solvent was removed and washed with DCM (2 x 10 mL). The p*H* of the reaction mixture was adjusted to 2 with 2 mL of 1N aq. HCl furnished the ketoacid (+)-**140aa/141aa** which extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried with Na_2SO_4 and crude product proceeded for next step.

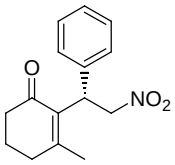
Second step: Ketoacid (+)-**140aa/141aa** (0.2 mmol) was dissolved in a mixture of concentrated HCl (0.2 mL) in THF (2.5 mL) and heated for 3 h at 90 ºC in a sealed glass tube. The mixture was concentrated and residue was partitioned between water and CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was chromatographed to yield 3-methyl-2-(2-nitro-1-phenylethyl)-cyclohex-2-enone (***R***)-**142aa** as yellow oil.

7c: Synthesis of 3-methyl-2-(2-nitro-1-phenylethyl)-cyclohex-2-enone (*S*)-142aa:

First step: In a 10 mL RB equipped with a magnetic stirring bar, to 0.33 mmol of 2-methyl-3-(2-nitro-1-phenylethyl)-4-oxo-cyclohex-2-enecarboxylic acid *tert*-butyl ester **133ba/134ba** was added 5 mL dry DCM as a solvent and then CH_3SO_3H (0.4 mL) was added dropwisely for 10 minits and the reaction mixture was stirred for 0.5 h at RT as indicated in Scheme 22. The mixture was partitioned between water and CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and concentrated and the crude product was proceded for next step.

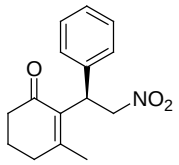
Second step: Ketoacid **140aa/141aa** (0.16 mmol) was dissolved in a mixture of concentrated HCl (0.5 mL) in THF (2 mL) and heated for 3 h at 90 °C in a sealed glass tube. The mixture was concentrated and residue was partitioned between water and CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was chromatographed to yield 3-methyl-2-(2-nitro-1-phenylethyl)-cyclohex-2-enone (***S*)-142aa** as yellow oil.

(1*S*)-3-Methyl-2-(2-nitro-1-phenylethyl)-cyclohex-2-enone (142aa): Prepared following the procedure **7c** and purified by column chromatography using EtOAc/hexane and isolated as a yellow liquid. The ee was determined by chiral-phase HPLC using a Daicel Chiralcel OD-H column (hexane/*i*-PrOH = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 12.2 min (major), t_R = 15.5 min (minor); **$[\alpha]^{25}_D$ = –15.5 (*c* 0.2, $CHCl_3$, 44% ee)**; IR (neat): ν_{max} 2926, 2857, 1663 (C=O), 1614, 1551, 1452, 1377, 1173 and 1055 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.31-7.22 (5H, m, Ar-*H*), 5.28 (1H, dd, *J* = 12.4, 8.8 Hz), 5.09 (1H, dd, *J* = 12.4, 6.4 Hz), 4.76 (1H, t, *J* = 6.4 Hz), 2.46-2.30 (4H, m), 2.11 (3H, s, olefinic-C*H*$_3$), 1.92 (2H, t, *J* = 6.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 198.7 (C, C=O), 160.3 (C), 139.0 (C), 133.4 (C), 128.7 (2 x CH), 127.6 (2 x CH), 127.1 (CH), 77.9 (CH_2), 42.5 (CH), 38.7 (CH_2), 33.8 (CH_2), 21.8 (CH_2), 21.7 (CH_3, olefinic-*C*H_3); LRMS m/z 260.10 ($M + H^+$), calcd $C_{15}H_{17}NO_3$ 259.1208; Anal. calcd for $C_{15}H_{17}NO_3$ (259.12): C, 69.48; H, 6.61; N, 5.40. Found: C, 69.35; H, 6.39; N, 5.52%.



(*S*)-**142aa**

(1*R*)-3-Methyl-2-(2-nitro-1-phenylethyl)-cyclohex-2-enone (142aa): Prepared following the procedure **7b** and purified by column chromatography using EtOAc/hexane and isolated as a yellow liquid. The ee was determined by chiral-phase HPLC using a Daicel Chiralcel OD-H column (hexane/*i*-PrOH = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 11.6 min (minor), t_R = 14.2 min (major); **$[\alpha]^{25}_D$ = +10.7 (*c* 0.3, $CHCl_3$, 33% ee)**; IR (neat): ν_{max} 2926, 2857, 1663 (C=O), 1614, 1551, 1452, 1377, 1173 and 1055 cm^{-1}.



(*R*)-**142aa**