RAPID SYNTHESIS OF DRUG-LIKE POLYCYCLIC SUBSTANCES: SCOPE OF COMBINING ORGANOCATALYSIS WITH METAL-CATALYSIS

A Thesis
Submitted for the Degree of

DOCTOR OF PHILOSOPHY

By

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December 2010

DEDICATED TO

MY FAMILY

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.*

RUMPA MONDAL

(Candidate)

CERTIFICATE

I hereby certify that the entire work embodied in this thesis has been carried out by ***Ms. Rumpa Mondal,*** *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)

DEAN
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CONTENTS

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PREFACE

Catalysis is the heart of most of the biologically important processes. A systematic evaluation and understanding of biochemical transformations inspired scientists to mimic these processes in synthesizing highly functionalized molecules with high selectivities. This in turn led to the development of organic synthesis catalyzed by small organic molecules as well as metal or metal ion complexes.

Although metal-free (organocatalysis) and metal-catalysis have their own advantages, none of them are omnipotent and efforts have been made to combine both these processes in multi-catalytic cascade fashion to carry out some exceptional transformations with ease. The present work is the fruit of relentless efforts made towards this aim.

*The present thesis entitled "**Rapid Synthesis of Drug-like Polycyclic Substances: Scope of Combining Organocatalysis with Metal-catalysis**" describes the synthesis of highly functionalized molecules in multi-catalytic cascade approach by combining enamine or iminium catalysis with metal (Cu, Ru) catalysis. 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.*

The first two chapters describe the synthesis of β-hydroxy carbonyls and β-alkoxy carbonyls which are widely occurring building blocks in a large spectrum of biologically active compounds, through enamine catalysis and iminium catalysis respectively. The revolutionary Barbas-List aldol reaction was utilized to synthesize a number of β-hydroxy carbonyls from different 2-alkynylbenzaldehydes and ketones, with high selectivities in good yields. Some unusual double aldol addition products were also isolated with high selectivities in moderate yields. On the other hand the direct addition of a variety of alcohols to enones was achieved by a combination of pyrrolidine/methane sulphonic acid through iminium catalysis in the absence of any added metal.

In the third chapter, a dimethylamino-ethanol/CuI-catalyst combination is employed for the first time towards a diversity oriented synthesis of 1,4-disubstituted [1,2,3]-triazoles through a cascade three-component Friedel–Crafts alkylation/Huisgen cycloaddition (FCA/HC) reactions of 2-naphthols, substituted isatins and azides.

In a similar manner, a combination of organocatalysis with copper-catalysis is explored for the synthesis of substituted indenes and 1,2,3-triazoles and these studies are the subject of the fourth chapter. A multi-catalytic cascade reaction of 2-ethynylbenzaldehydes, CH acids, organic hydrides and azides is realized in the presence of a catalytic amount of L-proline/CuI/Cs_2CO_3 or Et_3N or DIPEA. This methodology has been applied for the high-yielding synthesis of glucocorticoid receptor modulators.

In continuation of development of multi-catalytic cascade reaction, organo-catalysis is combined with Ru-catalysis to synthesize highly functionalized drug-like carbocycles. A one-pot sequential cascade TCRA/C-allylation/enyne-RCM/Diels-Alder reactions of 2-ethynyl-benzaldehydes, CH-acids, organic-hydrides, allyl bromide, diazomethane, reactive dienophiles under amino acid-/self-/base-/ruthenium-/thermal-catalyses affords functionalized polycyclic substances which are of considerable importance in biology and pharmaceutical industries.

LIST OF ABBREVIATIONS

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
DABCO	1,4-diazabicyclo(2.2.2)octane
DBU	1,8-diazabicyclo(5.4.0)undec-7-ene
DCM	dichloromethane
DCU	dicyclohexyl urea
dd	doublet of doublet
de	diastereomeric excess
DEPT	distortionless enhancement by polarization transfer
DMAP	dimethylaminopyridine
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
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
tert	tertiary
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl

ABOUT THE AUTHOR

The author, **Ms. Rumpa Mondal** was born on 22nd February 1982 in Kolkata, West Bengal. After her initial schooling, she obtained her B. Sc. degree in 2002 from Jadavpur University, Kolkata and she obtained her M. Sc. Degree with organic chemistry specialization in 2004 from the same University. She continued as a research scholar in the School of Chemistry, University of Hyderabad for the Ph. D. programme from July 2005 onwards. Presently she is working as a research associate in the department.

LIST OF PUBLICATIONS

1. D. B. Ramachary, **R. Mondal**, Direct organocatalytic hydroalkoxylation of α,β-unsaturated ketones, ***Tetrahedron Lett.*** **2006**, *47*, 7689–7693.
2. D. B. Ramachary, G. B. Reddy, **R. Mondal**, A new organocatalyst for Friedel–Crafts alkylation of 2-naphthols with isatins: application of an organo-click strategy for the cascade synthesis of highly functionalized molecules, ***Tetrahedron Lett.*** **2007**, *48*, 7618–7623.
3. D. B. Ramachary, **R. Mondal**, Rapid two-step synthesis of drug-like polycyclic substances by sequential multi-catalysis cascade reactions, ***Org. Biomol. Chem.*** **2010**, *8*, 321–325.
4. D. B. Ramachary, **R. Mondal,** Rapid synthesis of functionalized indenes, triazoles, and glucocorticoid receptor modulators by sequential multicatalysis cascade reactions, ***Eur. J. Org. Chem.*** **2010**, 3205–3210.
5. D. B. Ramachary, **R. Mondal,** Direct organocatalytic Barbas-List aldol reactions of 2-alkynylbenzaldehydes with ketones ***(to be communicated)***

POSTERS AND PRESENTATIONS

1. Given a flash oral presentation entitled “Rapid Two-step Synthesis of Highly Functionalized Polycyclic Substances by Sequential Multi-catalysis Cascade Reactions” in 7th in-house symposium **“Chemfest-2010***”* held at University of Hyderabad, Hyderabad, India during January 9-10, 2010.

RAPID SYNTHESIS OF DRUG-LIKE POLYCYCLIC SUBSTANCES: SCOPE OF COMBINING ORGANOCATALYSIS WITH METAL-CATALYSIS

1. ABSTRACT

A high-yielding asymmetric synthesis of β-hydroxy carbonyls with good diastereo- and enantioselectivities was achieved by Barbas-List aldol reaction of 2-alkynylbenzaldehydes with various ketones in the presence of *trans*-4-*OH*-L-proline or L-proline derived prolinamide catalyst at the ambient temperature or –35 °C. This method also gives access to some novel double aldol addition compounds, which are of medicinal importance.

An unprecedented direct addition of a variety of alcohols to *in situ* activated olefins was observed in the presence of mild bifunctional amine/acid catalysts at room temperature. The reactions proceed in the absence of transition metals by using simple commercially available catalysts, amines and acids. This constitutes an attractive

method for the preparation of β-alkoxy ketones, which are prevalent targets and intermediates in organic synthesis.

An expedient synthesis of highly functionalized 1,4-disubstituted [1,2,3]-triazoles was achieved by a cascade three-component Friedel–Crafts alkylation/Huisgen cycloaddition (FCA/HC) reactions of 2-naphthols, substituted isatins and azides under dimethylamino-ethanol/CuI-catalysis.

A general process for the synthesis of substituted indenes and 1,2,3-triazoles was achieved through a multicatalytic cascade reaction of 2-ethynylbenzaldehydes, CH acids, organic hydrides, and azides in the presence of a catalytic amount of L-proline/CuI/DIPEA. The potential of a single copper catalyst for catalyzing two different reactions was discovered and was applied to the high-yielding synthesis of glucocorticoid receptor modulators.

An efficient amino acid-/self-/base-/ruthenium-/thermal-catalyzed two-step process for the synthesis of functionalized drug-like carbocycles was achieved through combinations of cascade TCRA/*C*-allylation/enyne-RCM/Diels-Alder reactions as key steps starting from simple acyclic substrates. A combination of organocatalysis with ruthenium-catalysis provides route to a two-step synthesis of druglike carbocycles.

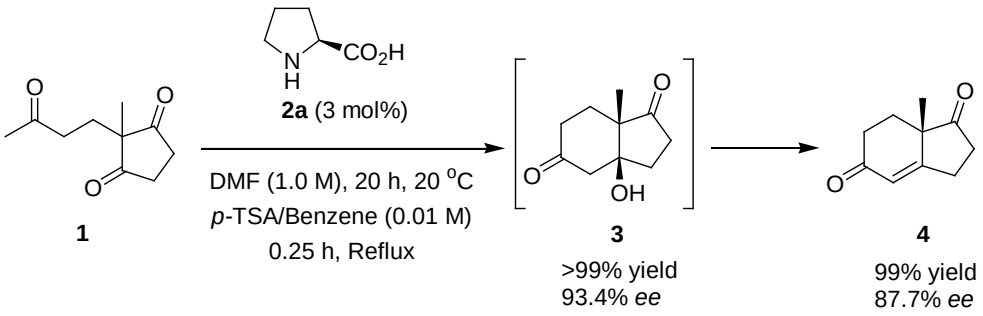
2. INTRODUCTION

The terminology “organocatalysis” introduced in the early days of this century, refers to the catalytic ability of small organic molecules containing C, N, S and O to carry out organic transformations, which were predominantly achieved by metal catalysis or enzymatic catalysis in the last century. Amines and amino acids are the most widely used organocatalysts, which operate mainly through two different activation modes, namely the enamine catalysis and the iminium catalysis.

As the research work described in this thesis deals with organocatalytic reactions involving both enamine and iminium ion intermediates[1] as well as their combinations with transition metal catalysis[2], a brief overview on sequential combination of both these strategies are presented below. The evolution of the concept of combining organocatalysis with metal catalysis is also described in a nutshell.

The chemistry of enamine has its root in the early 1950's when Stork *et al.* reported their elegant approach for α-alkylation and α-acylation of carbonyl compounds through the intermediacy of a pyrrolidine enamine.[3] With a basic understanding of the activation of carbonyl compounds towards nucleophilic substitution or addition reactions by primary or secondary amines, the following years witnessed some pioneering discoveries in the synthesis of naturally occuring molecules such as vitamins, steroids, terpenoids etc.[4]

Asymmetric synthesis of organic compounds employing catalytic amounts of amines or amino acids was achieved in 1974 by the group of Hajos and Parrish. Their original studies for the asymmetric aldol cyclodehydration reaction on **1** showed that only 3 mol% of L-proline **2a** was able to catalyze the aldol reaction in polar aprotic solvents like DMF, affording the intermediate aldol product **3** in high yield and *ee*, followed by acid catalysed dehydration to furnish **4** in 99% yield and 87.7% *ee* as shown in eq. 1.[5]



1 **3** **4**

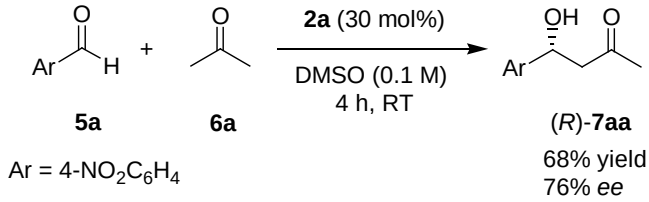
>99% yield
93.4% *ee*

99% yield
87.7% *ee*

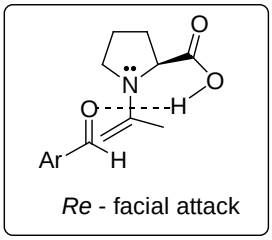
(1)

Their work could not emphasize the role of L-proline in this intramolecular aldol reaction, as such the mechanism was a matter of discussion for a long period of time until the early 21st century.

In 2000, Barbas and co-workers reported the first L-proline **2a** catalyzed direct asymmetric intermolecular aldol reaction of unmodified ketone **6a** and aromatic aldehyde **5a** affording the aldol adduct (*R*)-**7aa** in 68% yield with 76% *ee*. Based on thorough knowledge from their previous work on antibody catalyzed asymmetric direct aldol reactions, they envisaged the involvement of a proline-acetone enamine as the key intermediate in the above reaction mechanism, assigning L-proline as a "micro-aldolase".[6]

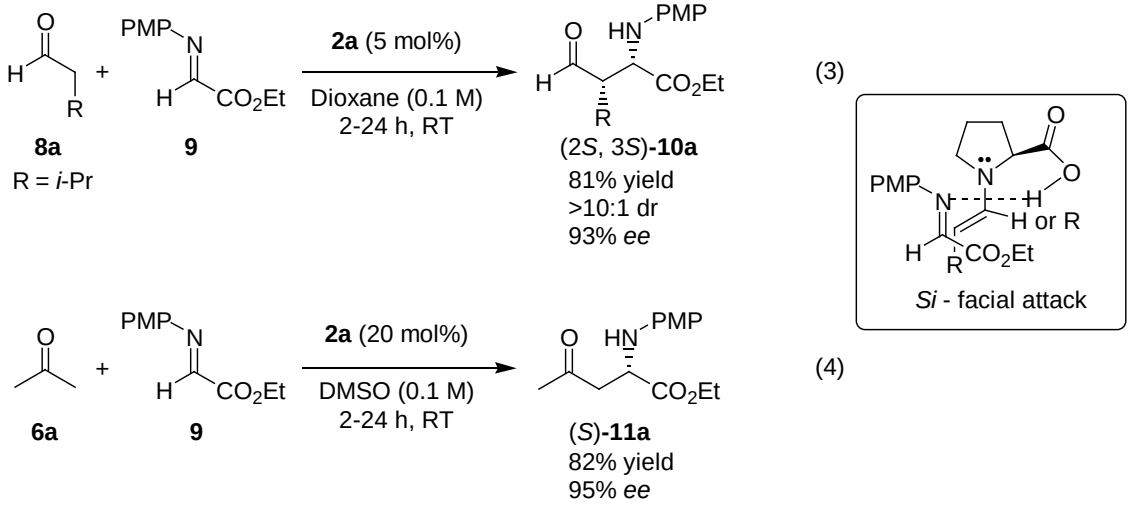


(2)



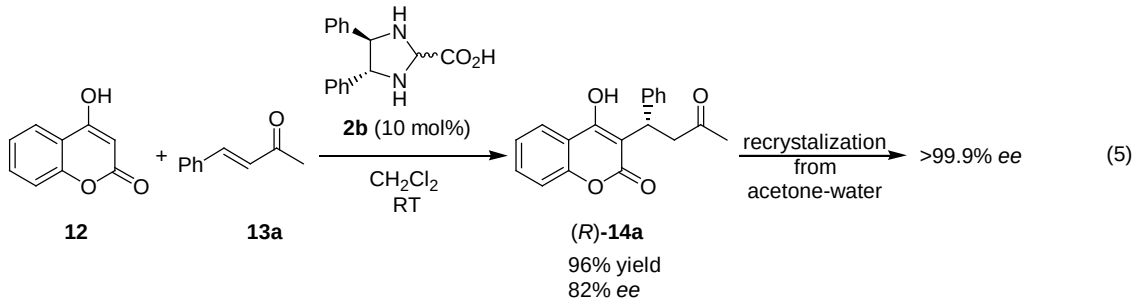
This discovery carved the niche for organocatalytic asymmetric synthesis involving enamine intermediates and organocatalysis continued to flourish following this pathway.

In continuation of developments, in 2003, Barbas and his co-workers reported direct Mannich type reactions involving *N*-PMP-protected α-imino ethyl glyoxylate **9** as the acceptor and unmodified aldehyde **8a** or ketone **6a** as donor. They showed that only 5-20 mol% of L-proline **2a** could catalyze these reactions in dioxane or DMSO solvents furnishing the products (*2S, 3S*)-**10a** and (*S*)-**11a** in good yields, excellent diastereoselectivities and enatioselectivities as depicted in eq. 3 and eq. 4.[7]

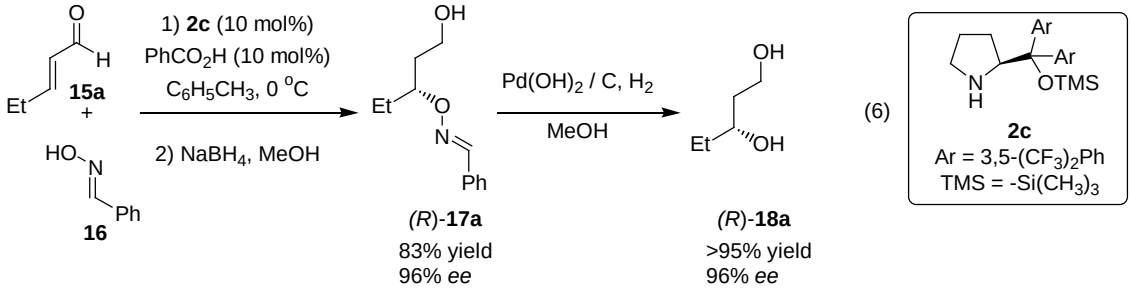


On the other hand, synthesis of organic compounds involving imines or iminium ions as active intermediates was known even by the early 20th century. As enamine catalysis evaded its way towards newer developments, people started revisiting the concept of iminium catalysis as another useful strategy for asymmetric synthesis using chiral secondary amines as organocatalysts.

In 2003, Jørgensen and his co-workers described the highly enantioselective synthesis of Warfarin, an important anticoagulant, from 4-hydroxycoumarin **12** and benzylideneacetone **13a** in one step using the iminium catalysis strategy. Warfarin (*R*)-**14a** was obtained in 96% yield with 82% *ee* employing 10 mol% of the imidazolidine catalyst **2b** and the optical purity of the product increased to >99.9% upon a single recrystalization from acetone-water as shown in eq. 5.[8]

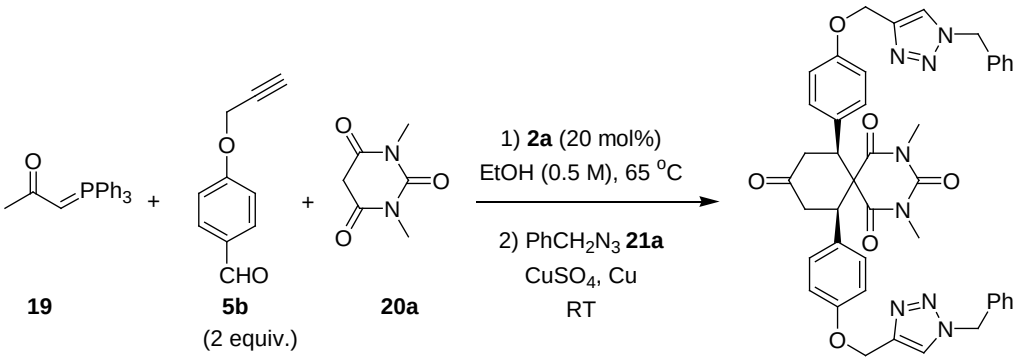


Iminium catalysis provided a route for another challenging transformation, the β-hydroxylation of α,β-unsaturated aldehydes, which was achieved by the group of Jørgensen in 2006. A combination of the chiral catalyst **2c** and benzoic acid (each 10 mol%) was shown to catalyze the addition of benzaldehyde oxime **16** to 2-*trans* pentenal **15a** at 0 °C. Subsequent reduction of the Michael adduct with $NaBH_4$ furnished the product (*R*)-**17a** in 83% yield with 96% *ee*. An easy removal of the oxime functionality by hydrogenation afforded the desired β-hydroxy product (*R*)-**18a** in >95% yield with 96% *ee* as depicted in eq. 6.[9]



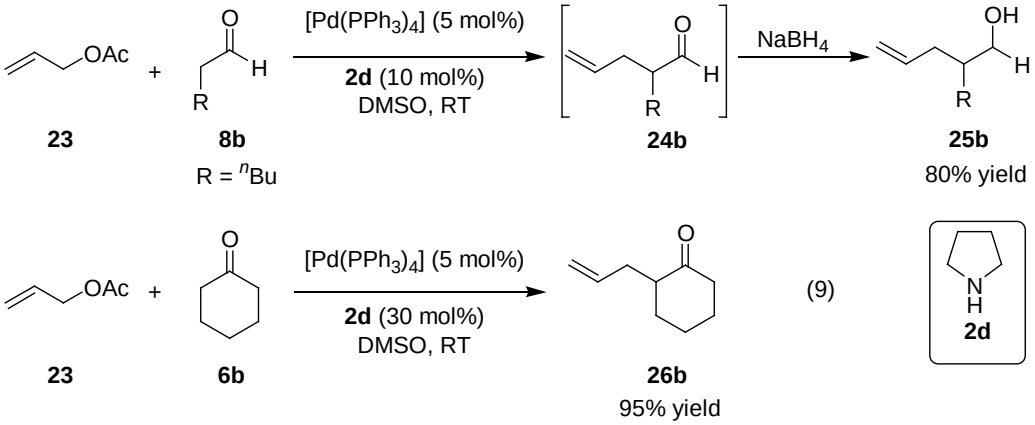
In a quest for synthesizing structurally complex molecules from simple readily available starting materials, multi-catalytic/multi-component reaction strategies were being introduced. The fact that the organic transformations which are unable to proceed in the presence of either organocatalysts or metal catalysts alone, could be accomplished by combining both these strategies in a multi-catalytic fashion, encouraged the scientists to look for compatible organocatalyst-metal catalyst systems.

In this context, in 2004, Ramachary and Barbas reported a high yielding synthesis of polysubstituted spirotrione-1,2,3 triazole **22baa** starting from simple commercially available materials like triphenylphosphoranylidene-2-propanone **19**, 2 equiv. of the aromatic aldehyde **5b,** *N*,*N*-dimethyl barbituric acid **20a** and benzylazide **21a** by a combination of L-proline and Cu^I catalysis through a sequence of Wittig/Knoevenagel/Diels-Alder/Huisgen 1,3 dipolar cycloaddition reactions in one-pot as depicted in eq. 7.[10]



(7)

In 2006, Córdova reported a direct chemoselective α-allylic alkylation of hexanal **8b** and cyclohexanone **6b** by allyl acetate **23** in presence of 10-30 mol% of pyrrolidine **2d** and 5 mol% of $Pd(PPh_3)_4$ through a combination of enamine catalysis and Pd-π-allylic activation in one-pot. The α-alkylated ketone **26b** was isolated in 95% yield whereas *in situ* reduction of the α-allylic aldehyde **24b** afforded the α-allylic alcohol **25b** in 80% yield (see eq. 8 and eq. 9).[11]

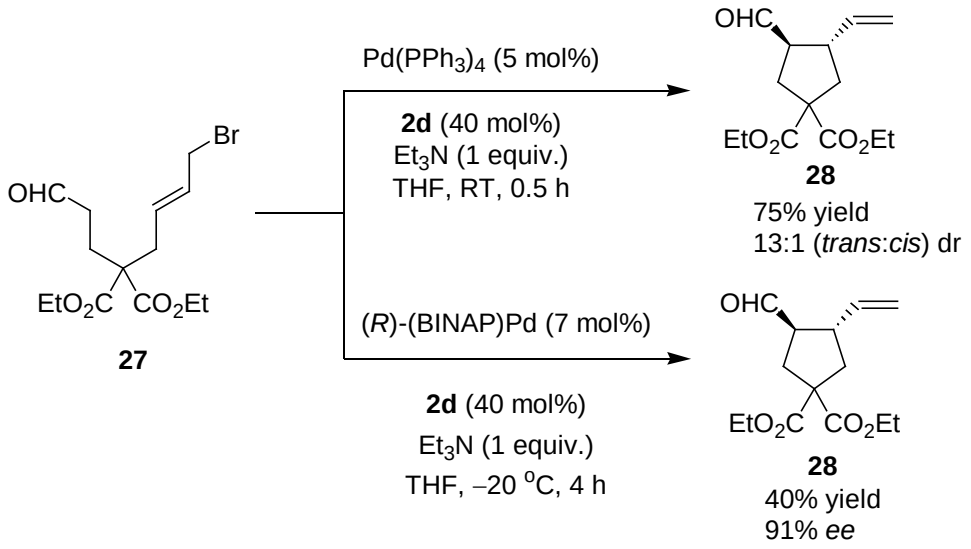


(8)

(9)

In 2007, Saicic *et al.* explored the above strategy for the intramolecular α-allylation of the aldehyde **27** containing the malonate moiety to furnish the 5-membered cyclic aldehyde **28** in 75% yield with 13:1(trans:cis) dr. The simultaneous activation of the aldehyde and the allylic moiety was achieved by 40 mol% of **2d** and 5 mol% of

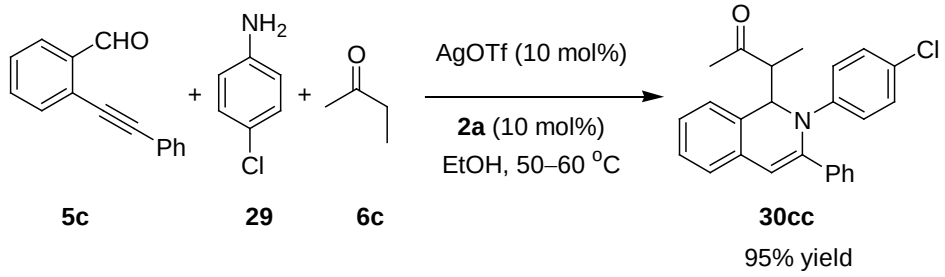
$Pd(PPh_3)_4$ as shown in eq. 10.[12] The same product **28** was isolated in 40% yield with 91% *ee* at –20 °C using a chiral catalyst (*R*)-(BINAP)Pd (7 mol%) in combination with 40 mol% of **2d** and 1equiv. of Et_3N as shown in eq. 11.[12]



(10)

(11)

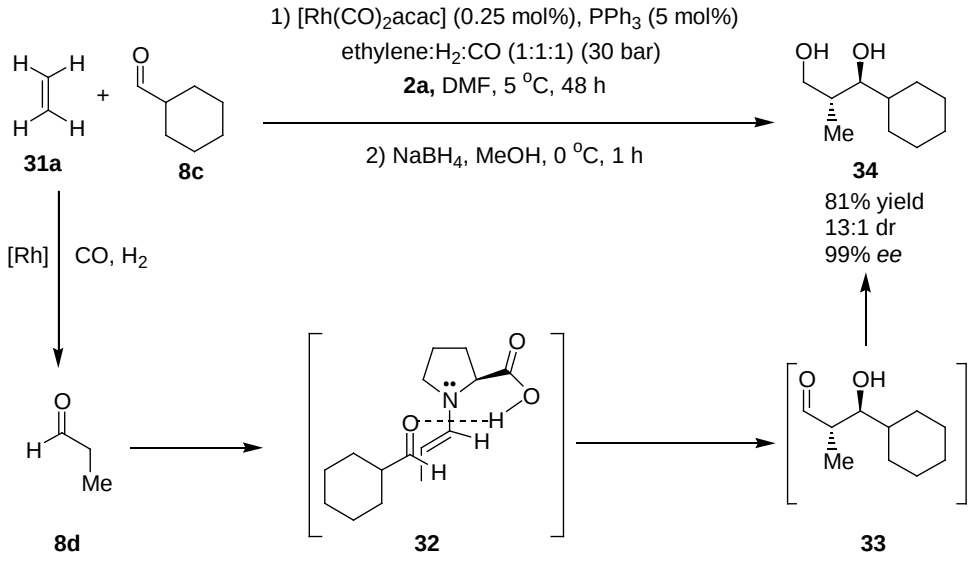
At the same time, Ding and Wu synthesized the highly functionalized 1,2-dihydroisoquinoline derivatives by a multi-component reaction. The 1,2-dihydroisoquinoline derivative **30cc** was isolated in 95% yield, starting from simple substrates like 2-phenylethynylbenzaldehyde **5c**, p-chloroaniline **29** and 2-butanone **6c** by a combination of soft lewis acid catalyst AgOTf (10 mol%) and organocatalyst L-proline **2a** (10 mol%) as depicted in eq. 12.[13]



(12)

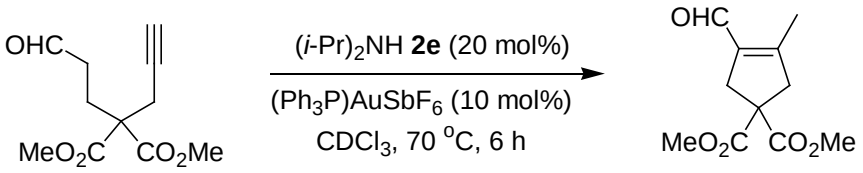
In 2007, Breit and his co-worker reported a one-pot domino Rh catalyzed hydroformylation reaction followed by L-proline catalyzed cross-aldol reaction to

synthesize valuable building blocks for polypropionate construction. By proper choice of the ligands, the rate of Rh catalyzed hydroformylation reaction of ethylene **31a** was controlled in such a way that the concentration of *in situ* generated propanal **8d** would be minimum, so that it would participate in a L-proline catalyzed cross-aldol reaction with cyclohexane carbaldehyde **8c** to furnish the product **33,** rather than undergoing a self-aldol reaction as illustrated in eq. 13.[14] *In situ* reduction of **33** afforded the final 1,3-diol product **34** in 81% yield with 13:1 (trans:cis) dr and 99% *ee*.



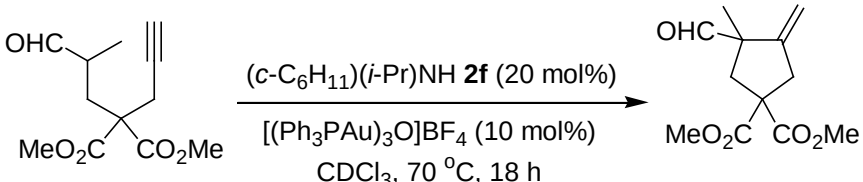
(13)

In 2008, Kirsch *et al*. demonstrated a direct carbocyclization of formyl alkyne **35** by using DIPA **2e** (20 mol%) and $(Ph_3P)AuSbF_6$ (10 mol%) as the optimal catalysts combination. A combined Au and enamine catalysis furnished the 5-exo-dig cyclization product, which *in situ* isomerized to the more stable alkene **36** in 82% yield (see eq. 14).[15] The same carbocyclization of α-substituted formyl alkyne **37** required the usage of cyclohexyl-isopropyl amine **2f** (20 mol%) and $[(Ph_3PAu)_3O]BF_4$ (10 mol%) to afford the isomeric formyl alkene **38** in 71% yield (see eq. 15).[15]



35 **36**
82% yield

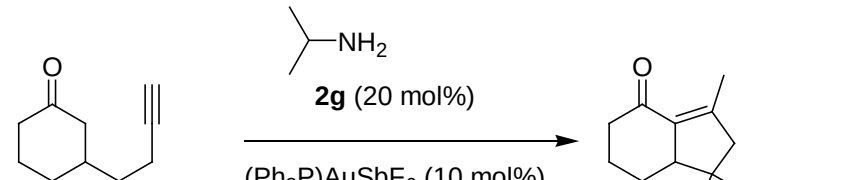
(14)



37 **38**
71% yield

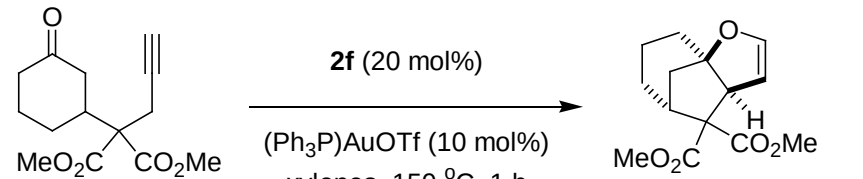
(15)

Cyclic ketone **39** also underwent similar carbocyclization reaction to furnish the product **40** in 74% yield catalyzed by (*i*-Pr)NH_2 **2g** (20 mol%) and $(Ph_3P)AuSbF_6$ (10 mol%) in $CDCl_3$ at 90 °C as illustrated in eq.16.[15] But eq. 17 shows that in presence of (c-C_6H_{11})(*i*-Pr)NH **2f** (20 mol%) and $(Ph_3P)AuOTf$ (10 mol%) in xylenes at 150 °C, the course of the reaction changed to a formal [3+2] cycloaddition reaction to afford the product **41** in 67% yield.[15]



39 **40**
74% yield

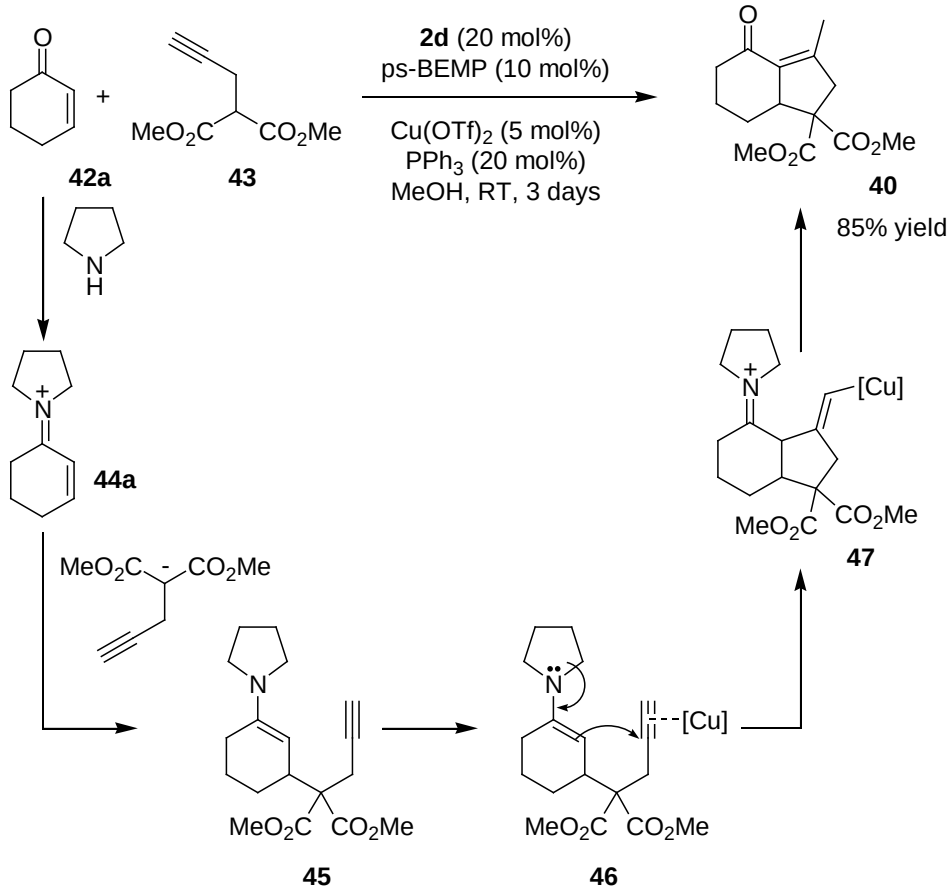
(16)



39 **41**
67% yield

(17)

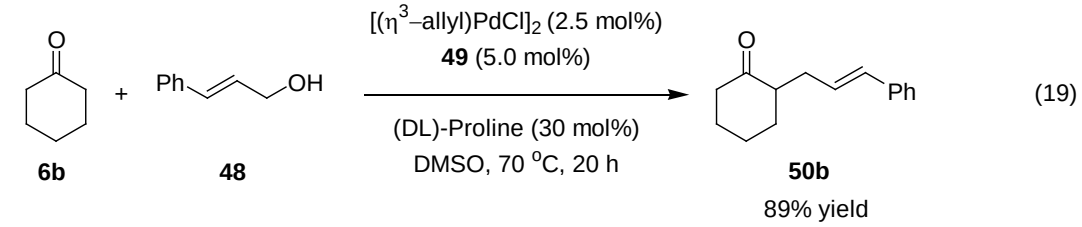
In 2008, Dixon and co-workers synthesized the same compound **40** through a sequential Michael addition, carbocyclization reaction of cyclohexenone **42a** with dimethylpropargylmalonate **43** by a combination of iminium, enamine and Cu^{I} catalyses. The reaction mechanism involved the formation of the intermediate iminium ion **44a** followed by Michael addition of the conjugate base of **43** to give the alkyne tethered enamine intermediate **45** which subsequently underwent carbocyclization (in the presence of *in situ* generated Cu^{I} species), protonolysis, hydrolysis and isomerisation to afford **40** in 85% yield as demonstrated in eq. 18.[16]



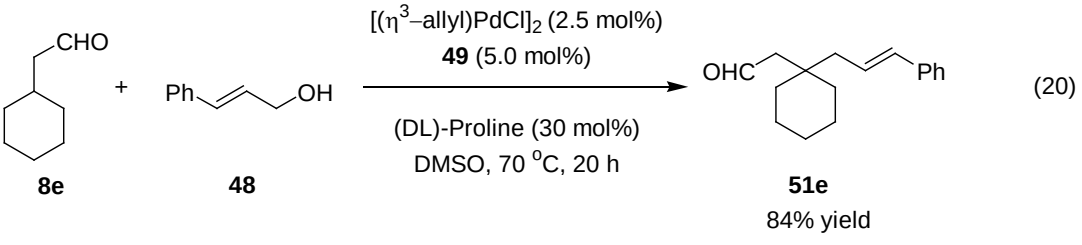
(18)

Later, in 2009, Breit *et al*. further explored the scope of combined enamine and Pd-π-allylic activation strategy for the α-allylation of enolizable ketone **6b** and aldehydes **8e** using cinnamyl alcohol **48**. They synthesized the compounds **50b** and **51e**

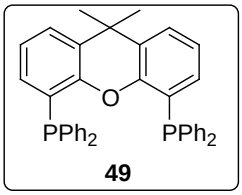
in 89% and 84% yields respectively, employing DL-proline as the organocatalyst and the diphosphine ligand, xantphos **49** for the generation of the active Pd-species from $[(\eta^3\text{-allyl})PdCl]_2$ as depicted in eq. 19 and eq. 20.[17]



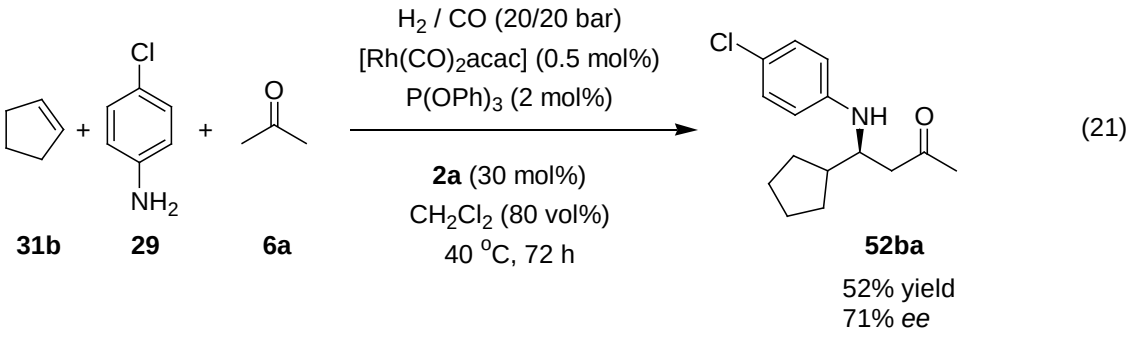
(19)



(20)

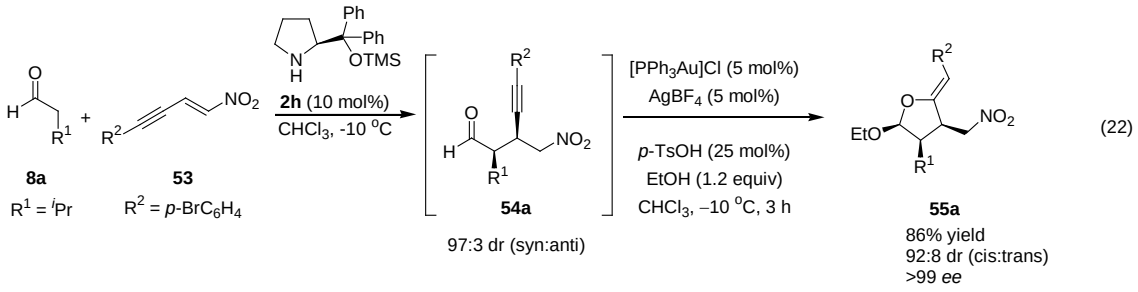


The concept of combined Rh and amine/amino acid catalysis was further extended by Eilbracht and his co-workers in 2009. They reported a tandem Rh catalyzed hydroformylation reaction of cyclopentene **31b** and L-proline catalyzed Mannich reaction of the *in situ* generated cyclopentanecarbaldehyde with p-chloroaniline **29** and acetone **6a** to furnish **52ba** in 52% yield and 71% *ee* as shown in eq. 21.[18]



(21)

In 2009, Alexakis *et al.* designed an excellent strategy to synthesize highly substituted tetrahydrofuran compounds by a one-pot combination of organocatalysis with Au catalysis. As shown in eq. 22, the reaction Scheme involved a **2h** catalyzed Michael addition of isopentanal **8a** to nitroenyne **53** affording the intermediate **54a** in 97:3 dr, followed by Au catalyzed acetalization/cyclization reaction in EtOH (1.2 equiv.) to furnish the nitro-substituted tetrahydrofuranyl ether **55a** in 86% yield, 92:8 ratio of the cis:trans diastereomers with >99% *ee*.[19]



(22)

As we are interested in the development of sequential one-pot combination of organocatalysis with metal-catalysis, research work has been carried out to utilize organocatalytic strategies for the synthesis of basic building blocks as well as highly functionalized molecules starting from simple materials by combination of organocatalysis with metal-catalysis and the results are presented in this thesis.

To begin with, asymmetric organocatalytic Barbas-List aldol reaction[20] was revisited to synthesize β-hydroxy ketone moiety which are widely occurring building blocks in many natural products and the results are presented in the next section.

3. DIRECT ORGANOCATALYTIC BARBAS-LIST ALDOL REACTIONS OF 2-ALKYNYLBEZALDEHYDES WITH KETONES

3.1 INTRODUCTION

Although the potential of L-proline to catalyze asymmetric intramolecular aldol reaction was known since long back,[5] the pioneering discovery of L-proline catalyzed direct intermolecular asymmetric aldol reaction of aromatic aldehydes with acetone by Barbas, List and co-workers,[6] opened a new gateway for organocatalytic asymmetric reactions. Following this "Barbas-List Aldol (BLA)" reaction pathway, the last decade has seen a tremendous development in the field of "organocatalytic asymmetric aldol reactions" both in terms of catalyst designing as well as reaction engineering. A vast number of organocatalysts, mostly based on the L-proline moiety has been synthesized and utilized under finely tuned reaction conditions to provide aldol products with high selectivities in both aqueous and organic media with broad range of substrates. The transition state of the BLA reaction has been studied extensively providing evidences for an enamine based mechanism where hydrogen-bonding plays a key role to achieve the high enantioselectivity.[21]

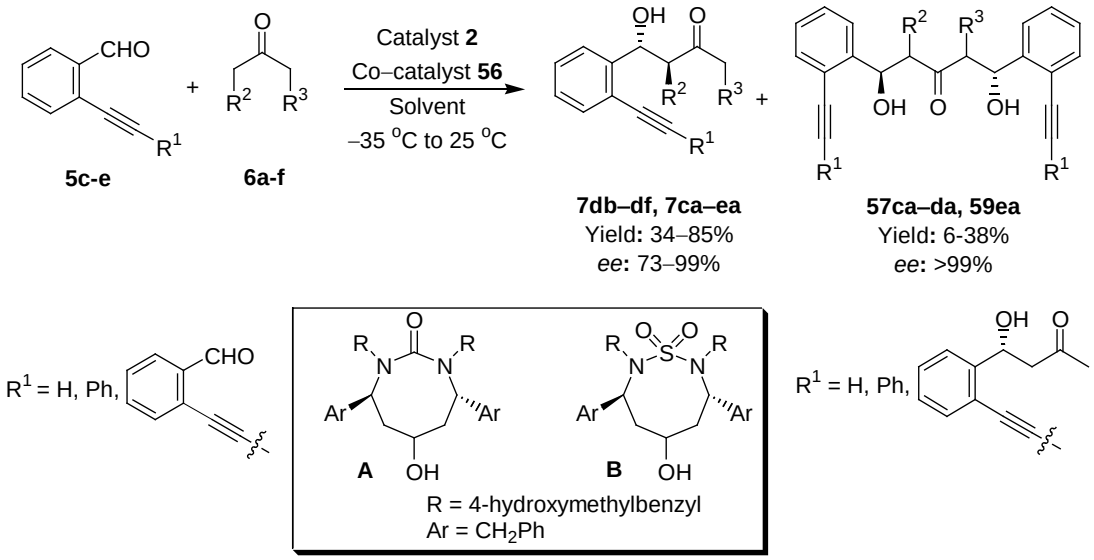
In BLA reactions, mainly an aldehyde acts as the acceptor or the electrophile and a ketone or another aldehyde acts as the donor or nucleophile. The scope of a large number of aliphatic and aromatic aldehydes has been explored so far as the acceptor in the BLA reaction with both acyclic and cyclic ketone donors, providing aldol products with high diastereo- and enantioselectivities using different organocatalysts. As expected, aromatic aldehydes containing electron withdrawing groups at the *ortho* or *para* position are "highly reactive" towards any nucleophile and furnish the aldol adducts with high yields and high selectivities. Whereas, the presence of electron donating groups at the *ortho* or *para* position decreases both the reactivity and

selectivity. Moreover, the reactivity of the aldehydes, in some instances, considerably affect the product ratio leading to the formation of double aldol addition products along with the mono aldol addition products from "highly-reactive" aromatic aldehydes.[22] But high yielding asymmetric synthesis of 1,5-dihydroxy-pentan-3-one (double aldol addition) products from "less-reactive" aromatic aldehydes are rare in organocatalysis.

As a matter of fact, aromatic aldehydes containing electron donating or neutral *ortho* groups are much less explored in organocatalytic aldol reactions. It was envisaged that both the electronic and stereochemical properties of the group at the *ortho* position of aromatic aldehyde play a crucial role in the transition state of the organocatalytic aldol reaction and therefore can significantly controle the selectivity of the aldol products. Hence, aldol reactions of aromatic aldehydes containing *ortho* groups could be an interesting subject to study in organocatalysis.

As a part of ongoing research in our laboratory on organocatalytic asymmetric synthesis,[20, 23] the scope of 2-alkynylbenzaldehydes as acceptor in organocatalytic BLA reaction with various cyclic and acyclic ketones was studied and the findings are disclosed in the next section (Scheme 1). The expected aldol adducts were obtained with high yields and high *ee* s, as well as in some cases 1,5-dihydroxy-pentan-3-one (double aldol addition) derivatives were isolated as the major product with *ee* >99%. Therefore these studies also give an insight into the highly enantioselective synthesis of 1,5-dihydroxy-pentan-3-one derivatives from "less reactive" aromatic aldehydes. These double aldol addition products can be utilized for the synthesis of 8-membered cyclic urea and cyclic sulfamide, analogous to **A** and **B** which are regarded as potent HIV-1 protease inhibitors (see Scheme 1).[24]

Scheme 1: Direct organocatalytic BLA reaction of 2-alkynylbenzaldehydes **5c-e** with ketones **6a-f**



HIV-1 PROTEASE INHIBITORS

3.2 RESULTS AND DISCUSSIONS

The study was initiated employing a number of known and novel organocatalysts (Figure-1), L-proline **2a** being the first choice as it is unequivocally accepted as the universal asymmetric catalyst.

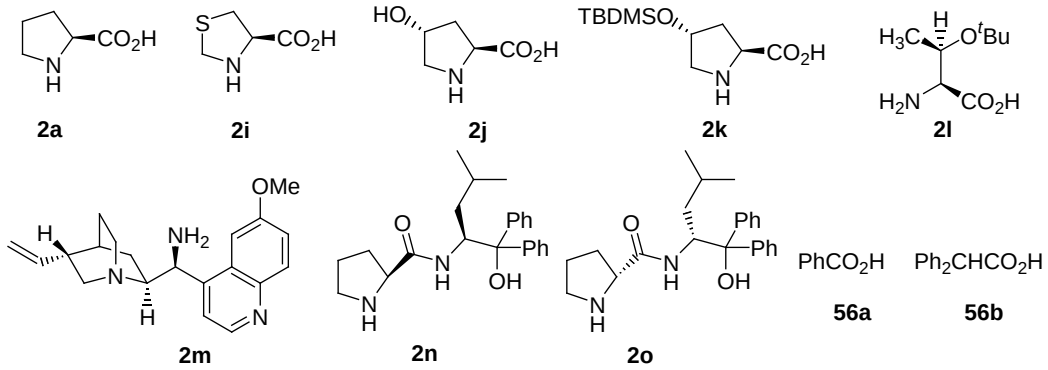
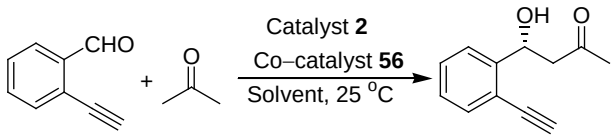


Figure-1: Structures of catalysts and co-catalysts studied in the BLA reaction

Optimization was carried out by varying the reaction conditions and some of the results are summarized in Table 1. It was observed that 20 mol% of L-proline **2a** was able to catalyze the reaction between 2-ethynylbenzaldehyde **5d** and 34 equiv. of acetone **6a** in DMSO at 25 °C to give the desired BLA adduct **7da** in 84% yield with 60% *ee* within 1 h (Table 1, entry 1). The same BLA reaction of **5d** with 34 equiv. of **6a** under 20 mol% of **2a** catalysis at 25 °C for 2 h using DMF or NMP as solvent, also gave similar results. In DMF, **7da** was furnished in 87% yield with 65% *ee* while in NMP the yield and *ee* were 85% and 68% respectively (Table 1, entries 2 and 3). CH_3CN proved to be inferior as compared to other polar aprotic solvents in the above reaction and afforded **7da** in only 35% yield with 59% *ee* under similar reaction conditions even after longer reaction time. Replacing the catalyst L-proline **2a** with thiaproline **2i** (20 mol%) for the reaction of **5d** with **6a** in DMSO for 24 h at 25 °C furnished **7da** in low yield albeit with 71% *ee* (Table 1, entry 5). Interestingly, when the BLA reaction of **5d** with 34 equiv. of **6a** was catalyzed by 20 mol% of *trans*-4-*OH*-L-proline **2j** in DMSO at 25 °C, the aforesaid product **7da** was isolated with 85% yield and 73% *ee* (Table 1, entry 6).

The BLA adduct **7da** was isolated with comparable yields and *ee s* when catalyzed by *trans*-4-*OH*-L-proline **2j** under similar reaction conditions in both DMF and NMP solvents (Table 1, entries 7 and 8). *trans*-4-*OTBDMS*-L-proline **2k** (20 mol%) also afforded the product **7da** in 82% yield with 66% *ee* in DMSO solvent within 7 h. When the amount of acetone **6a** was reduced from 34 equiv. to 14 equiv., then also the BLA adduct **7da** was obtained with an optical purity of 71% but at the expense of yield (74%) under **2j** catalysis in DMSO (Table 1, entry 10). Use of acyclic amino-acid, O-*t*-Bu-L-threonine **2l** as a catalyst in the above BLA reaction in DMSO, did not appear to be promising, furnishing **7da** in only <10% yield even after 24 h. The bifunctional catalyst Q-NH_2 **2m**/Ph_2CHCO_2H **56b** also gave similar result in the above reaction (Table 1, entry 12).

Table 1: Optimization of the direct aldol reaction of **5d** with **6a**



5d **6a** **7da**

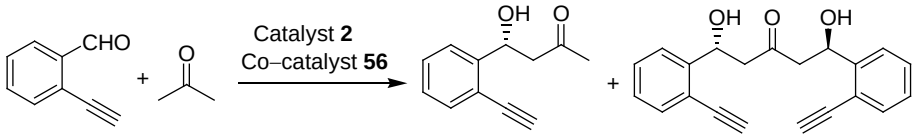
Entry	Catalyst **2** / Co–catalyst **56**	Solvent (0.125–0.3 M)	*t* (h)	Yield (%)[a]	*ee* (%)[b]
1[c]	**2a**	DMSO	1	84	60
2[c]	**2a**	DMF	2	87	65
3[c]	**2a**	NMP	2	85	68
4[c]	**2a**	CH_3CN	24	35	59
5[c]	**2i**	DMSO	24	25	71
6[c]	**2j**	**DMSO**	**24**	**85**	**73**
7[c]	**2j**	DMF	19	87	67
8[c]	**2j**	NMP	19	83	74
9[c]	**2k**	DMSO	7	82	66
10[d]	**2j**	DMSO	9	74	71
11[c]	**2l**	DMSO	24	<10	–
12[e]	**2m / 56b**	DCM	72	<10	–

[a]Yield refers to the column purified products. [b]*Ee* was determined by CSP HPLC analysis. [c]Reactions were carried out in solvent (0.125 M) with 34 equiv. of **6a** relative to **5d** (0.3 mmol) in the presence of 20 mol% of catalyst **2**. [d]Reaction was carried out in solvent (0.25 M) with 14 equiv. of **6a** relative to **5d** (0.3 mmol) in the presence of 20 mol% of catalyst **2**. [e]Reaction was carried out in solvent (0.3 M) with 28 equiv. of **6a** relative to **5d** (0.3 mmol) in the presence of each 10 mol% of catalyst **2m** and co-catalyst **56b**.

Among the various L-prolinamide catalysts developed for intermolecular asymmetric aldol reactions till date, the best results were achieved by Yun-Dong Wu and V. K. Singh *et al*. by using a small class of prolinamides where the acidity and strong hydrogen-bonding capacity of the catalyst guide the selectivity.[25] Inspired by these results, the catalyst **2n** was chosen for testing the BLA reaction of 2-

ethynylbenzaldehyde **5d** with acetone **6a**. Unexpectedly, when **5d** was treated with **6a** (0.3 M) using 10 mol% **2n** as a catalyst at 25 °C, the BLA product was formed in only 68% yield with 65% *ee* (Table 2, entry 1). Addition of 10 mol% $PhCO_2H$ **56a** as a co-catalyst for the same reaction under identical reaction conditions did not improve the yield or *ee* of the product **7da** (Table 2, entry 2).

Table 2: Further optimization of the BLA reaction of **5d** with **6a** using prolinamide catalysts **2n** and **2o**



5d **6a** **7da** **57da**

Entry	Catalyst **2**	Co–catalyst **56**	T (^oC)	*t* (h)	Yield (%)[a]		*ee* (%)[b]	
					7da	**57da**	**7da**	**57da**
1[c]	**2n**	–	25	6	68	–	65	–
2[d]	**2n**	**56a**	25	2	59	–	54	–
3[c]	**2n**	–	–35	28	20	44	65	>99
4[d]	**2n**	**56a**	–35	24	34	38	93	>99
5[d]	**2o**	**56a**	–35	24	16	29	-95	> –99

[a]Yield refers to the column-purified products. [b]*Ee* was determined by CSP HPLC analysis. [c]Reactions were carried out in neat acetone (0.3 M) with 10 mol% of catalyst **2n**. [d]Reactions were carried out in neat acetone (0.3 M) with each 10 mol% of catalysts **2n** or **2o** and co-catalyst **56a**.

Surprisingly, lowering the reaction temperature from 25 °C to –35 °C, had a profound impact on the outcome of the above reaction. It was pleasing to find that the reaction of **5d** with **6a** (0.3 M) catalyzed by 10 mol% of **2n** at –35 °C, not only furnished the expected BLA adduct **7da** in moderate yield and *ee* but also the double aldol addition product **57da** was isolated in 44% yield with >99% de and >99% *ee*, which is so far the highest optical purity obtained for the 1,5-dihydroxy-pentan-3-one derivatives (Table 2, entry 3). When the reaction was carried out using each 10 mol%

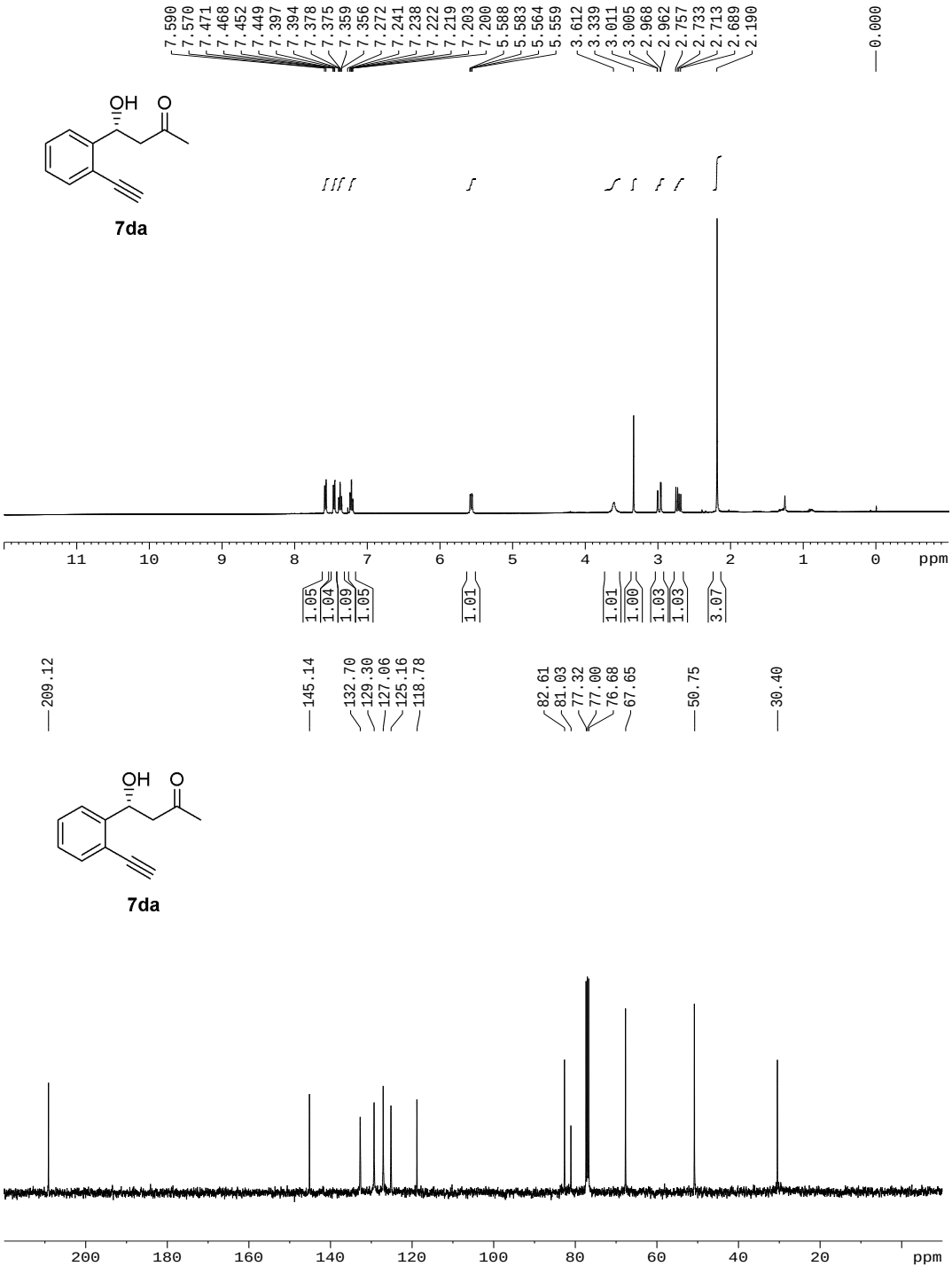


Figure-2: ^{1}H and ^{13}C NMR spectra of the product **7da**

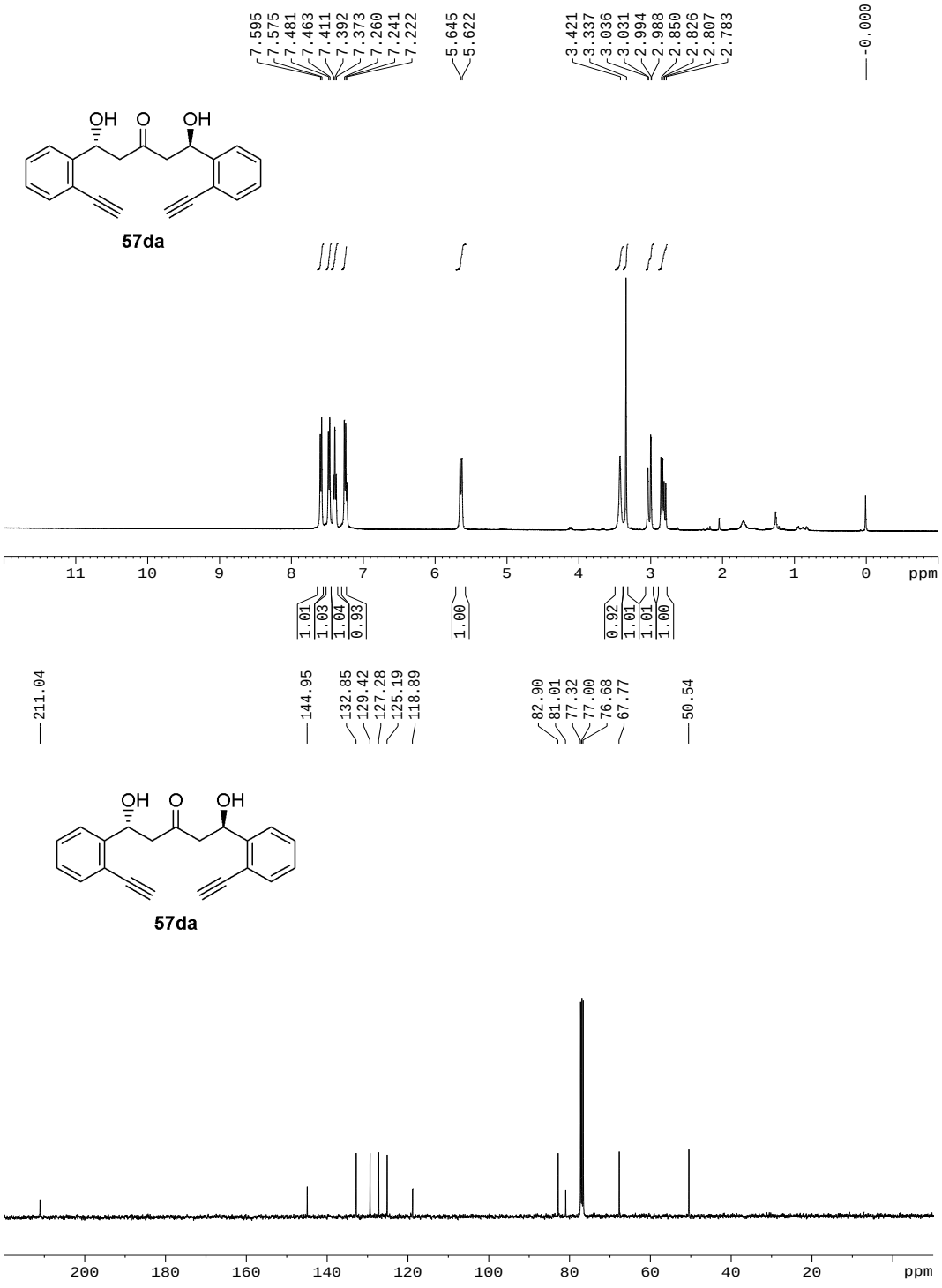
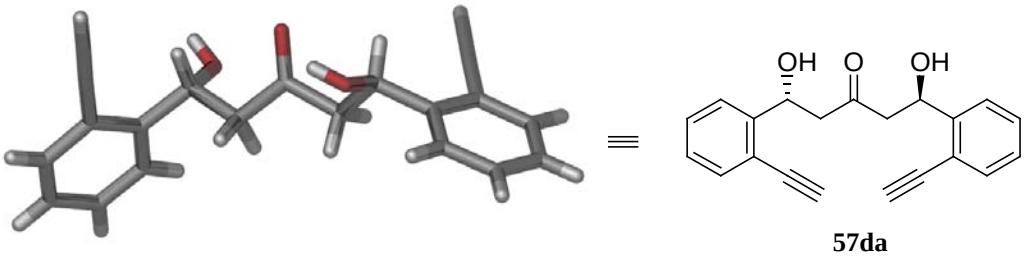


Figure-3: ^{1}H and ^{13}C NMR spectra of product **57da**

of the catalyst **2n** and co-catalyst **56a** in neat acetone (0.3 M) at –35 °C for 24 h, the BLA adduct **7da** was furnished with an improved 34% yield and 93% *ee* accompanied by **57da** in 38% yield with >99% *ee* (Table 2, entry 4). The catalyst **2o** (10 mol%) in combination with **56a** (10 mol%) also catalyzed the same reaction under identical reaction conditions to afford the opposite enantiomers of **7da** and **57da** with high *ee* s albeit with less yields (Table 2, entry 5). The structure of the product **57da** was determined by NMR analysis and the absolute configuration was confirmed by X-ray structure analysis (see Figure-4).[26]



57da

Figure-4: Crystal structure of 1,5-bis-(2-ethynylphenyl)-1,5-dihydroxy-pentan-3-one (**57da**)

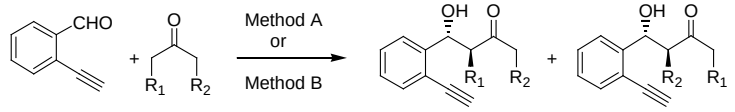
Therefore, two optimized reaction conditions were finalized for the BLA reaction of 2-ethynylbenzaldehyde **5d** with acetone **6a**. Method-A involved the usage of 20 mol% of **2j** as the catalyst at 25 °C in DMSO (0.125 M) solvent, whereas in method-B, the reaction was carried out at –35 °C using each 10 mol% of the catalyst **2n** and co-catalyst **56a** in neat acetone **6a** (0.3 M).

With the optimized reaction conditions in hand, the scope of other acyclic and cyclic ketones **6b-f** as donors in the BLA reaction with **5d** was also explored and the

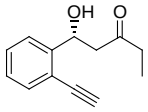
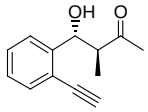
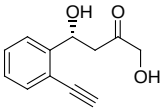
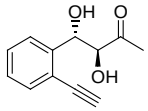
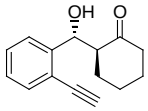
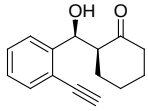
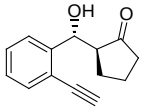
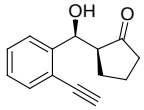
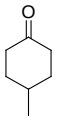
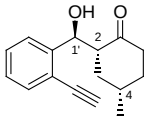
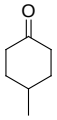
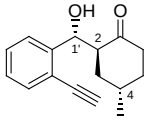
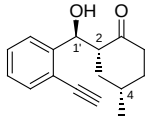
results are summarized in Table 3. The reaction of 2-ethynylbenzaldehyde **5d** with 2-butanone **6c** (0.3 M) catalyzed by **2n**/**56a**, each 10 mol% at –35 °C for 24 h furnished only the mono aldol addition products **7dc** and **58dc**. Interestingly, even though no double aldol addition product was observed in the above reaction, the regioselectivity, diastereoselectivity, yields and optical purities of the mono aldol addition products were excellent (Table 3, entry 1). Similarly, hydroxyacetone **6d** also reacted with **5d** under identical reaction conditions to afford the mono aldol addition products **7dd** and **58dd** in 25% and 61% yields respectively with moderate diastereomeric ratio of *anti*-**58dd** over *syn*-**58dd** but with poor enantioselectivities (Table 3, entry 2).

When 2-ethynylbenzaldehyde **5d** was treated with cyclohexanone **6b** (0.3 M) in presence of 10 mol% of **2n** and 10 mol% of **56a** at –35 °C, the expected BLA adduct **7db** was formed in 83% yield with a diastereomeric ratio of 11.6:1 in favour of *anti*-**7db**. The *ee* s of the products *anti*-**7db** and *syn*-**7db** were 96% and 91% respectively (Table 3, entry 3). Similarly, cyclopentanone **6e** (0.3 M) also reacted with **5d** following method-B to afford the products *anti*-**7de** and *syn*-**7de** in 72% yield with 1:1.89 dr (*anti*:*syn*). Though the optical purity of *anti*-**7de** was 95%, *syn*-**7de** was found to be almost racemic (Table 3, entry 4). Structures and regioselectivities of products **7** were obtained based on the NMR analyses and also by correlation with previous L-proline catalyzed aldol reactions.[25]

Table 3: Direct aldol reaction of 2-ethynylbenzaldehyde **5d** with various acyclic and cyclic ketones **6b-f**



5d **6b–f** **7db–df** **58dc–dd**

Entry	Ketone	t (h)	Products	Yield (%)[a]	dr[b] anti : syn	*ee* (%)[c] anti	*ee* (%)[c] syn
1[d]	 **6c**	24	 **7dc** (major)  **58dc** (minor)	71 (23)[e]	>99:1	99 (>99)[f]	–
2[d]	 **6d**	30	 **7dd** (minor)  **58dd** (major)	61 (25)[e]	2.5:1	15	2
3[d]	 **6b**	24	 *anti*–**7db**  *syn*–**7db**	83	11.6:1	96	91
4[d]	 **6e**	60	 *anti*–**7de**  *syn*–**7de**	72	1:1.89	95	0
5[d]	 **6f**	24	 **(*2R, 4S, 1'S*)–7df**	66	>99:1	81	–
6[g]	 **6f**	72	 ***(2S, 4S, 1'R)*–7df**  **(*2R, 4S, 1'S*)–7df**	53	1:1.24	70(82)[h]	–

[a]Yield refers to the column-purified products. [b]Dr was determined by NMR analysis on crude products. [c]*Ee* was determined by CSP HPLC analysis. [d]Method-B: Reactions were carried out in neat ketone (0.3 M) with each 10 mol% of catalysts **2n** and co-catalyst **56a** at –35 °C. [e]Values in parentheses refer to the yields of the minor regioisomers. [f]Value in parentheses refers to the *ee* of the minor regioisomer. [g]Method-A: Reaction was carried out in DMSO (0.125 M) in presence of 20 mol% of **2j** at 25 °C. [h]Value in parentheses refers to the *ee* of the minor diastereomer.

Finally, the desymmetrization of 4-methyl-cyclohexanone **6f** was studied using the BLA reaction of **5d** with **6f** following both method-A and B. The possible modes of attack and the structures of all possible stereoisomers of the BLA adduct **7df** under L-proline catalysis are depicted in Figure-5. Reaction of **6f** with **5d** following method-B, led to the formation of the single diastereomer (*2R, 4S, 1'S*)-**7df** in 66% yield with 81% *ee* (Table 3, entry 5). But when the same reaction was carried out following method A, the diastereomers (*2S, 4S, 1'R*)-**7df** and (*2R, 4S, 1'S*)-**7df** were formed in 1:1.24 ratio in 53% yield with 82% and 70% *ee* s respectively. The absolute configuration of the products (*2R, 4S, 1'S*)-**7df** and (*2S, 4S, 1'R*)-**7df** were assigned based on analogy with literature reports[27] and further studies are underway to assign the configuration unambiguously.

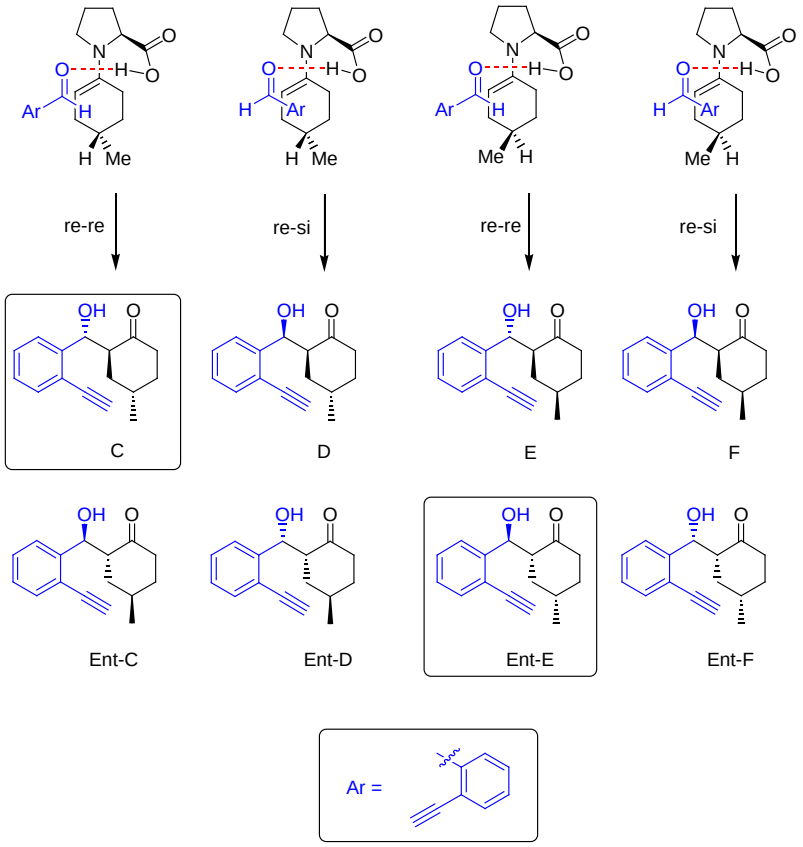


Figure-5: All possible stereoisomers of **7df**

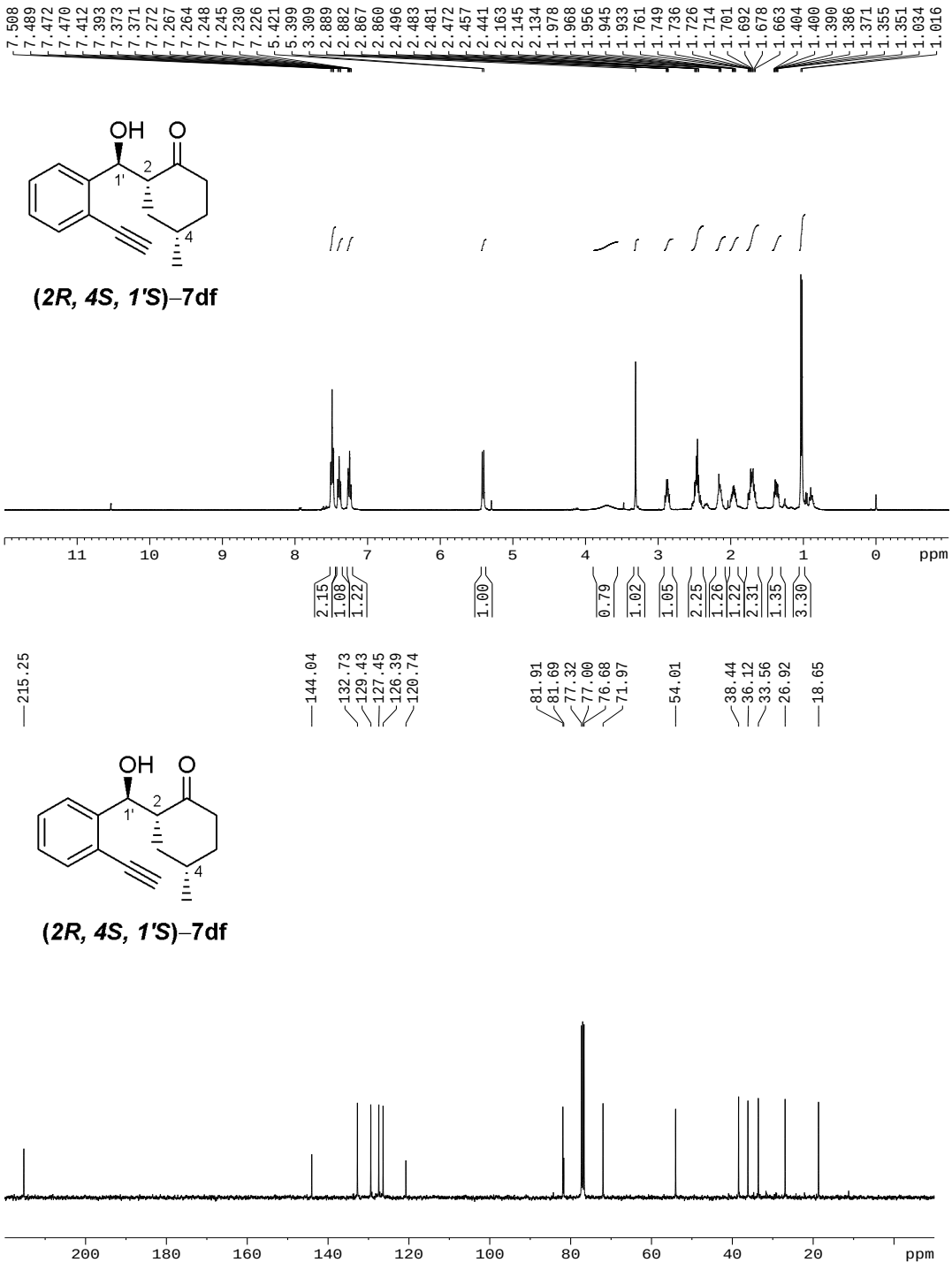
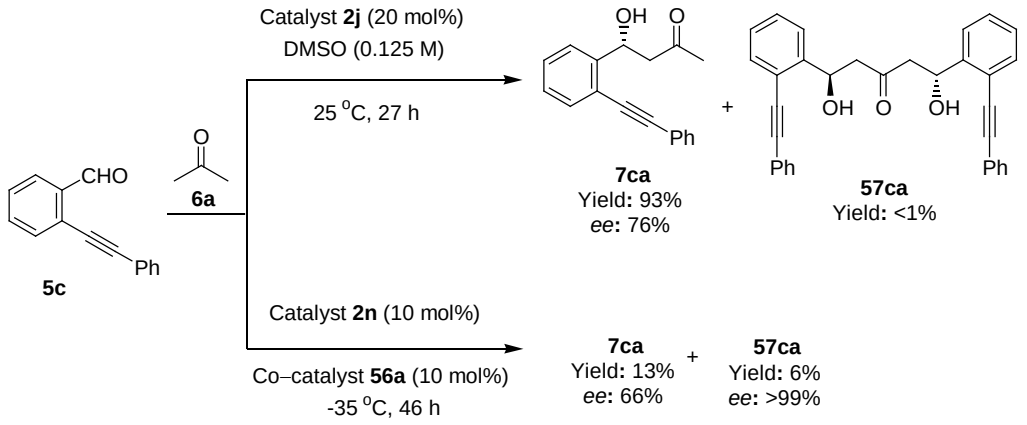


Figure-6: ^{1}H and ^{13}C NMR spectra of the product (*2R, 4S, 1'S*)-**7df**

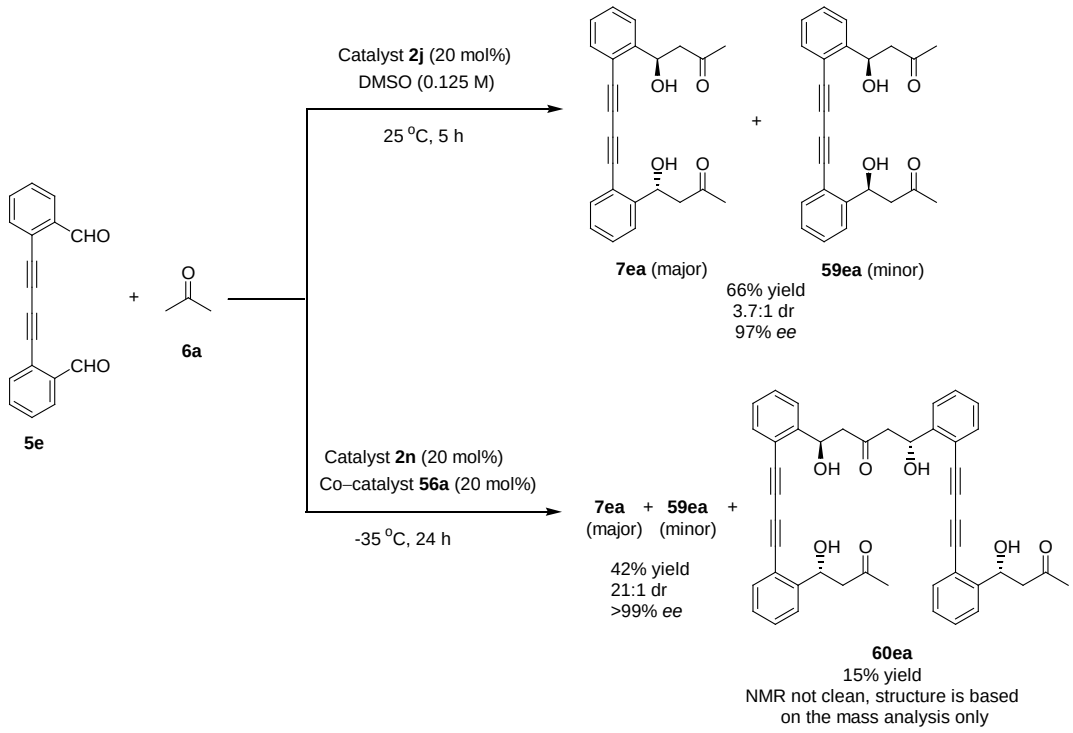
After successful demonstration of the BLA reaction of **5d** with various acyclic and cyclic ketones **6a-f**, different substituted alkynylbenzaldehydes **5c** and **5e** were also studied as acceptors for the BLA reaction with acetone as donor. As expected, 2-phenylethynylbenzaldehyde **5c** reacted with 34 equiv. of acetone **6a** under **2j** catalysis at 25 °C in DMSO to afford the desired product **7ca** in 93% yield with 76% *ee*. The same reaction when catalyzed by each 10 mol% of the catalyst **2n**/co-catalyst **56a** at –35 °C under neat condition (0.3 M), furnished the BLA adduct **7ca** in only 13% yield with 66% *ee* accompanied by trace amount (6%) of the double aldol addition product **57ca** with >99% *ee* (Scheme 2).

Scheme 2: Direct aldol reaction of 2-phenylethynylbenzaldehyde **5c** with acetone **6a**



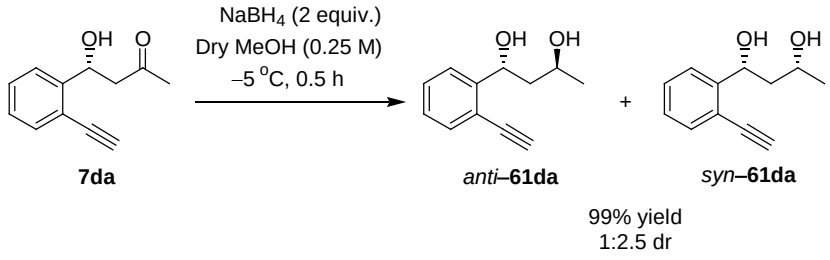
The BLA reaction of the diyne-dialdehyde **5e** with 34 equiv. of acetone **6a,** catalyzed by 20 mol% of **2j** at 25 °C in DMSO afforded the novel diyne-dialdol products **7ea** and **59ea** in 66% yield with 3.7:1 dr (**7ea:59ea**) and 97% *ee*. Interestingly, when the same reaction was carried out using method-B, another novel double aldol addition product **60ea** was isolated in 15% yield along with the formation of **7ea** and **59ea** in 42% yield, 21:1 dr (**7ea:59ea**) and >99% *ee*. The structure of the minor compound **60ea** was confirmed based on high resolution mass spectral analysis and NMR spectrum of this minor compound is not clear.

Scheme 3: Direct aldol reaction of Di-yne di-aldehyde **5e** with acetone **6a**



The BLA adduct **7da** was converted to the diols *anti*-**61da** and *syn*-**61da** in 99% yield with 1:2.5 dr by 2 equiv. of $NaBH_4$ in dry MeOH (0.25 M) at –5 °C within 0.5 h. as synthetic application.

Scheme 4: $NaBH_4$ reduction of BLA product **7da** to diols *anti*-**61da** and *syn*-**61da**



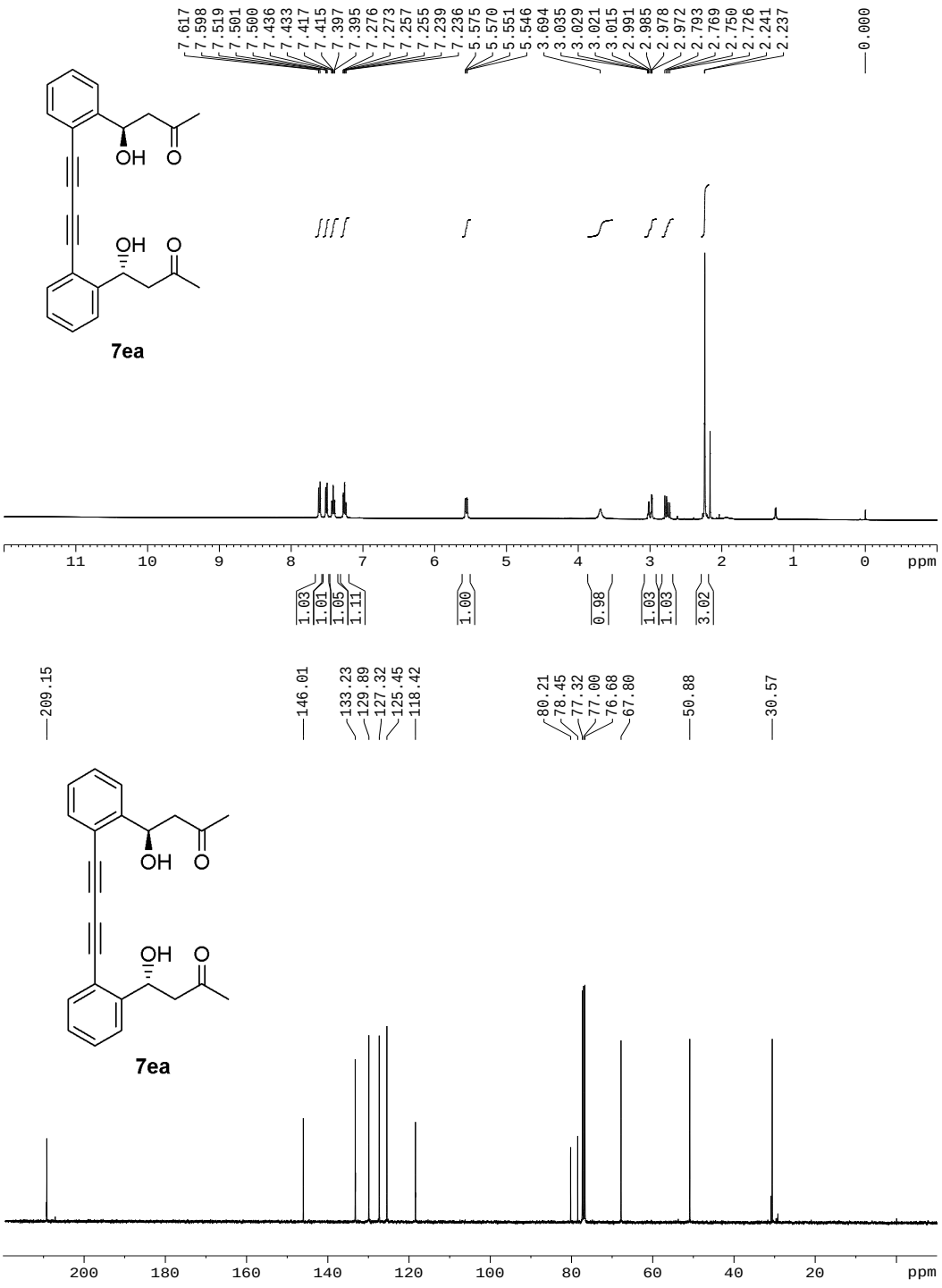


***Figure-7*:** ^{1}H and ^{13}C NMR spectra of the product **7ea**

3.3 CONCLUSION

In summary, the organocatalytic BLA reaction of 2-alkynylbenzaldehydes with various ketone donors was studied. In some cases, the formation of expected BLA adducts was accompanied by some novel double aldol addition products in moderate to good yields with high *ee* s. The potential of the BLA adducts has been demonstrated in the synthesis of chiral diols and the 1,5-dihydroxy-pentan-3-one derivatives can be utilized as potential HIV-1 protease inhibitor precursors.

4. DIRECT ORGANOCATALYTIC HYDROALKOXYLATION OF α,β-UNSATURATED KETONES

4.1 INTRODUCTION

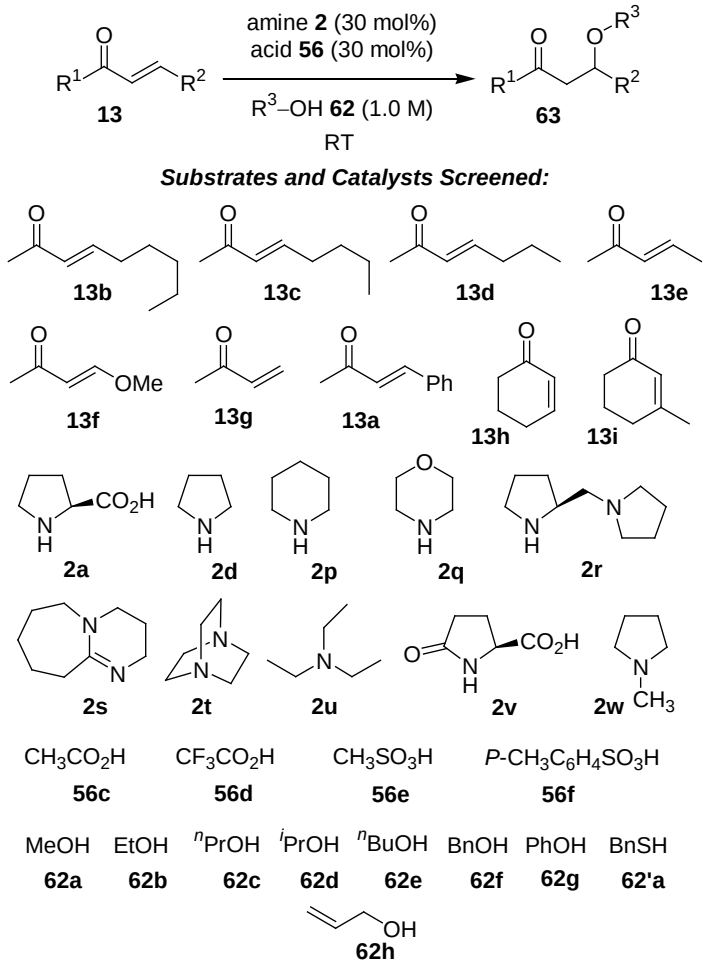
β-Hydroxy ketones and their alkoxy analogues are very important as valuable building blocks and structural motifs in a variety of natural products and in organic synthesis.[28] They are typically prepared either via aldol chemistry or sequential epoxidation and reduction of enones.[29] Direct preparation by addition of water to an enone is an attractive alternative, but only one method exists for this transformation.[30] Similarly, preparation of β-alkoxy ketones also represents a challenging problem in synthetic organic chemistry. Such hydroalkoxylation additions of alcohols to α,β-unsaturated ketones, aldehydes or esters promoted by several catalysts such as PMe_3,[30] DBU,[31] Tf_2NH,[32] $P(RNCH_2CH_2)_3N$[33] and transition metal complexes have been reported recently.[34] However, the hydroalkoxylation addition of alcohols to α,β-unsaturated ketones still remains a challenge, mainly because of the lower reactivity of alcohols and also due to the greater number of applications of the resulting products.

On the other hand, hydroalkoxylation reactions of other highly reactive heteroatom nucleophiles such as thiols[35] and amides[36] to more reactive α,β-unsaturated aldehydes via iminium ion intermediates have recently been realized by amine/acid bifunctional catalysts. In this context, developing a novel and 'green' amine/acid bifunctional catalyst for the oxy-Michael addition reaction of less reactive alcohols to α,β-unsaturated ketones via iminium ion catalysis would be an interesting task.

Recently, bifunctional amine/acid-catalysis has emerged as a powerful synthetic tool for the development of both achiral and chiral catalyzed condensations, cycloadditions, 1,2- and 1,4-additions of enals, enones and ketones with many

electrophiles.[37] It was reasoned that this catalysis strategy might be applicable to the *in situ* generation and conjugate addition of highly activated olefins if a suitable nucleophilic alcohol was present. Such a process would constitute a metal-free, green hydroalkoxylation of enones. Hence, a general and green metal-free synthetic method for the hydroalkoxylation of enones and other α,β-unsaturated substrates **13** by use of an amine/acid **2**/**56** as a bifunctional catalyst, was developed and the results are disclosed in the following section (Scheme 5).

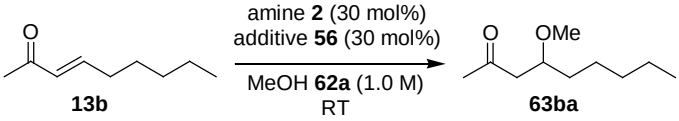
Scheme 5: Direct organocatalytic hydroalkoxylation of α,β-unsaturated ketones **13**



4.2 RESULTS AND DISCUSSIONS

During investigations on organo-catalyzed Diels–Alder[38] reactions of enones **13** in MeOH, it was observed that MeOH itself was undergoing Michael addition to enones **13** under proline catalysis. In the presence of catalytic amounts of proline, the direct addition of MeOH to non-3-en-2-one **13b** was realized with moderate conversion (Table 4, entry 1).

Table 4: Optimization of the organocatalytic hydromethoxylation of non-3-en-2-one **13b** with MeOH **62a**[a]



13b **63ba**

Entry	Amine **2**	Additive **56**	Time/h	Yield (%)[b]
1	Proline **2a**	–	12	57
2[c]	Proline **2a**	DBU **2s**	5	32
3[c]	Proline **2a**	DABCO **2t**	5	20
4[c]	Proline **2a**	Et_3N **2u**	5	20
5	Pyrrolidine **2d**	–	6	23
6[d]	Piperidine **2p**	–	16	<5
7[d]	Morpholine **2q**	–	12	<5
8	Diamine **2r**	–	11	40
9	Pyrrolidine **2d**	HCl	12	20
10	Pyrrolidine **2d**	CH_3CO_2H **56c**	12	25
11	Pyrrolidine **2d**	CF_3CO_2H **56d**	12	20
12	Pyrrolidine **2d**	*p*-TSA **56f**	22	50
13	Pyrrolidine **2d**	CH_3SO_3H **56e**	17	73
14	Piperidine **2p**	CH_3SO_3H **56e**	16	70
15	Morpholine **2q**	CH_3SO_3H **56e**	12	45
16	Diamine **2r**	CH_3SO_3H **56e**	11	45
17	–	DBU **2s**	12	64
18	–	CH_3SO_3H **56e**	17	58
19[e]	Pyrrolidine **2d**	CH_3SO_3H **56e**	28	64
20[d]	Pyroglutamic acid **2v**	–	17	–
21	N-Methylpyrrolidine **2w**	CH_3SO_3H **56e**	8	55

[a]30 mol% each of amine **2** and additive **56** were mixed at the same time, to this MeOH **62a** and enone **13b** were added at room temperature. [b]Yield refers to the column purified product. [c]Longer reaction times led to decomposition. [d]Enone **13b** was recovered. [e]10 mol% each of pyrrolidine **2d** and CH_3SO_3H **56e** were used as catalyst.

A number of organic amines, amine/base and amine/acid were tested as catalysts considering the hydromethoxylation of non-3-en-2-one **13b** as a benchmark at room temperature (Table 4). Pyrrolidine/CH_3SO_3H **2d/56e** (Table 4, entries 13 and 19) were the best catalysts for hydromethoxylation of **13b** compared to other catalysts such as amines **2a, 2p-v** (Table 4, entries 5–8), acid **56e** (Table 4, entry 18) and other amine/acid bifunctional catalysts **2/56** (Table 4, entries 9–12, 14–16 and entry 21). When the catalyst **2d/56e** loading was reduced from 30 mol% to 10 mol% for the hydromethoxylation of enone **13b**, the product yield decreased even after longer reaction times (Table 4, entry 19). Pyroglutamic acid **2v** did not catalyze the oxy-Michael reaction of **13b** with **62a** (Table 4, entry 20) and this is a good support for iminium ion catalysis rather than for acid/base catalysis.

Next, the scope and limitations of the hydroalkoxylation reaction of non-3-en-2-one **13b** with a range of alcohols **62a–h** and benzyl thiol **62'a** was explored under pyrrolidine/CH_3SO_3H-catalysis at room temperature (Table 5). As shown in Table 5, larger alkyl alcohols **62c–e** furnished hydroalkoxylation products **63bc–be** in lower yields compared to smaller alkyl alcohols **62a–b** in oxy-Michael reactions which may be due to moderate steric hindrance with larger alkyl groups. Benzyl alcohol **62f** furnished hydrobenzyloxy product **63bf** in moderate yield but phenol **62g** gave a poor conversion under identical conditions (Table 5, entry 7). Benzyl thiol **62'a** furnished the expected Michael product **63'ba** in good yield (Table 5, entry 9) and allyl alcohol **62h** furnished the expected hydroallyloxylation product **63bh** in moderate yield (Table 5, entry 8).

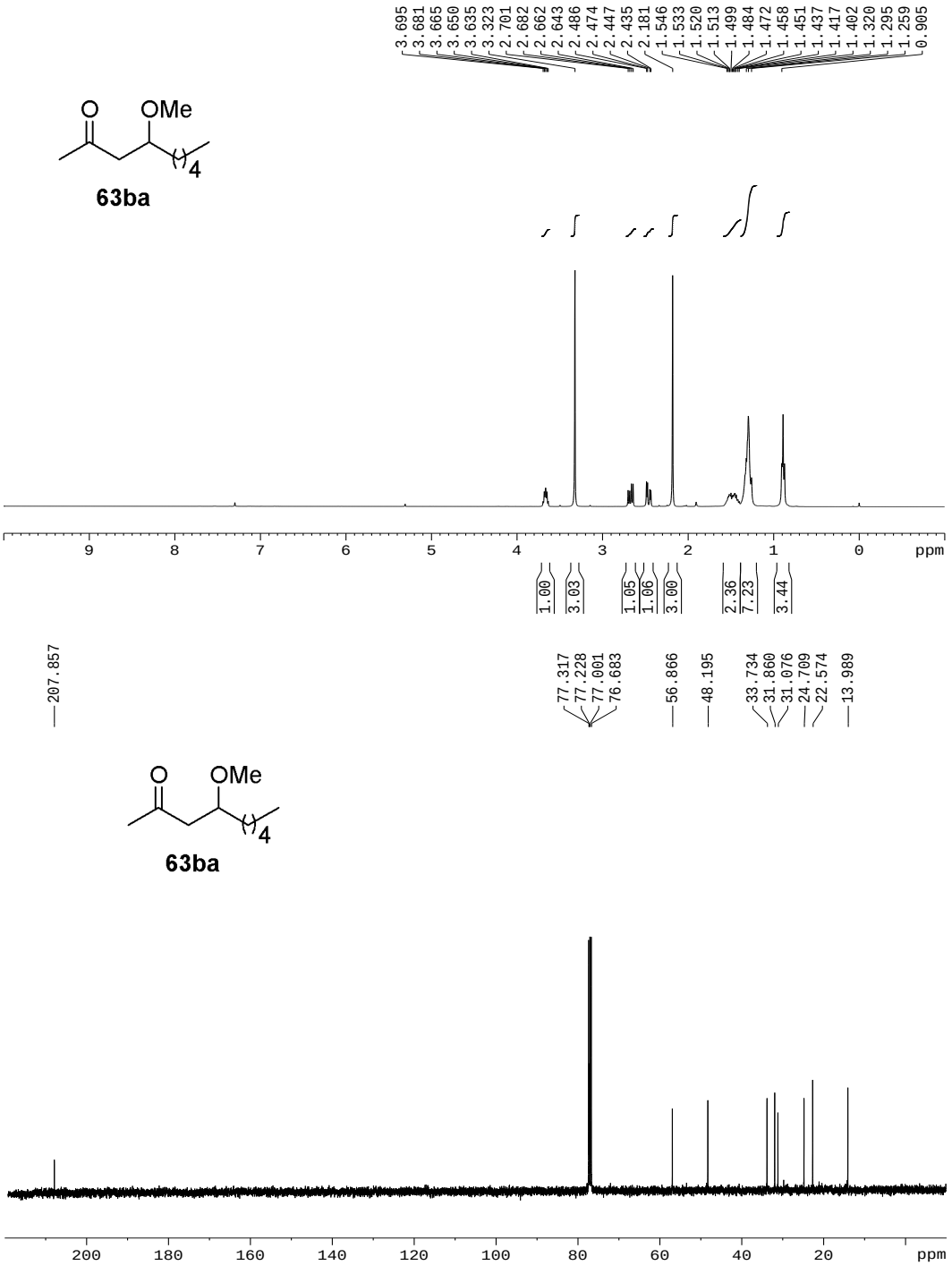


Figure-8: ^{1}H and ^{13}C NMR spectra of the product **63ba**

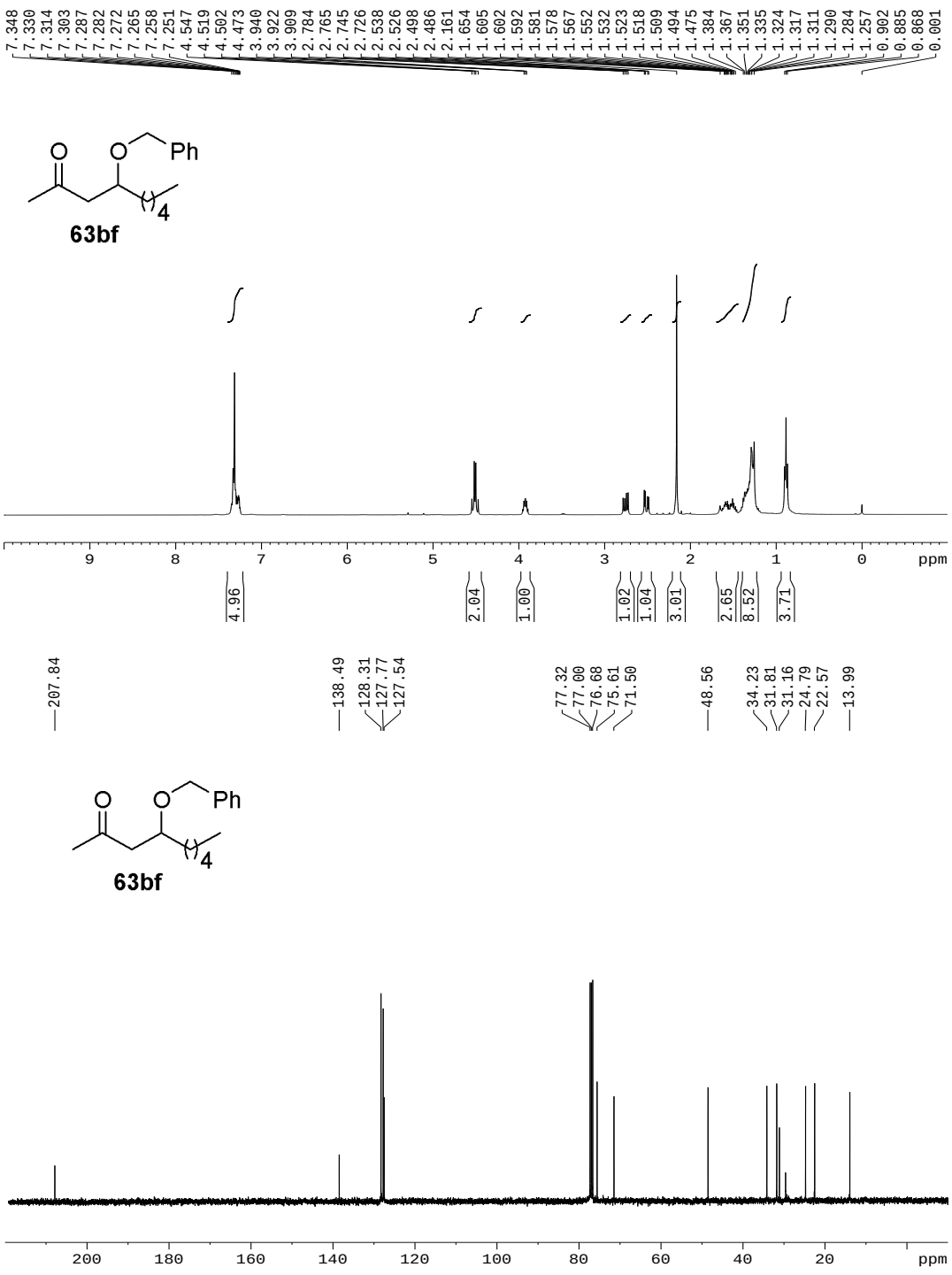
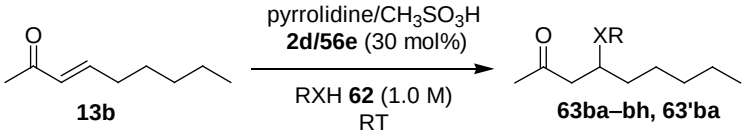


Figure-9: ^{1}H and ^{13}C NMR spectra of the product **63bf**

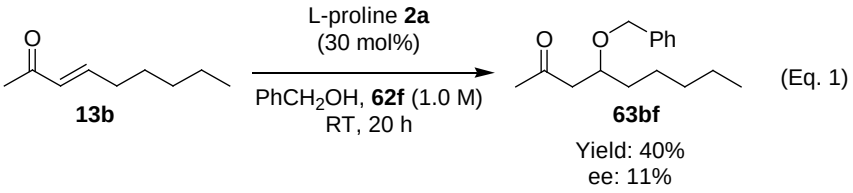
Table 5: Optimization of the organocatalytic hydroalkoxylation of non-3-en-2-one **13b** with various alcohols **62a-h** and benzyl thiol **62'a**[a]



Entry	RXH	Time/h	Product	Yield (%)[b]
1	MeOH, **62a**	17	**63ba**	73
2	EtOH, **62b**	21	**63bb**	51
3	^{n}PrOH, **62c**	37	**63bc**	48
4	^{i}PrOH, **62d**	66	**63bd**	21
5	BuOH, **62e**	37	**63be**	<3
6	$PhCH_2OH$, **62f**	12	**63bf**	45
7	PhOH, **62g**	49	**63bg**	<3
8	CH_2=$CHCH_2OH$, **62h**	96	**63bh**	50
9	$PhCH_2SH$, **62'a**	25	**63'ba**	77

[a]30 mol% each of amine **2d** and additive **56e** were mixed at the same time, to this alcohol **62a–h** or thiol **62'a** and enone **13b** were added at room temperature. [b]Yield refers to the column purified product.

To access the asymmetric induction in these reactions, hydrobenzyloxylation of enone **13b** with benzyl alcohol **62f** under L-proline **2a** catalysis was carried out furnishing the expected product **63bf** in 40% yield, but with only 11% *ee* as shown in Eq. 1.



(Eq. 1)

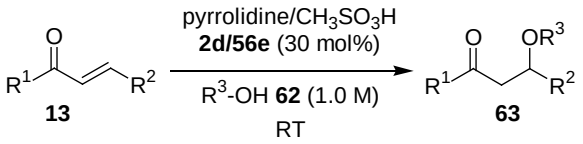
Synthesis of several hydroalkoxylation products **63** from different enones **13a–h** and alcohols **62a–c** under pyrrolidine/CH_3SO_3H **2d/56e**-catalysis was accomplished. The results in Table 6 indicate the broad scope of this novel methodology covering a structurally diverse group of enones **13a–h** and alcohols **62a–c** with many of the yields

obtained being very good or indeed better than previously published reactions starting from the corresponding enones **13**.

As shown in Table 6, the enones oct-3-en-2-one **13c**, hept-3-en-2-one **13d** and pent-3-en-2-one **13e** furnished hydromethoxylated **63ca–ea** and hydroethoxylated **63cb–eb** products from methanol and ethanol, respectively, in good yields (Table 6, entries 1–6). 4-Methoxy-but-3-en-2-one **13f** gave the useful organic intermediates, dimethyl acetal **63fa**, diethyl acetal **63fb'** and dipropyl acetal **63fc'** in very good yields by reaction with MeOH, EtOH and *n*-PrOH, respectively, as shown in Table 6, entries 7–9. Interestingly, hydroalkoxylation of **13f** with EtOH and *n*-PrOH furnished the unexpected acetals **63fb'** and **63fc'** as the major products rather than the expected acetals **63fb** and **63fc** which can be explained by amine/acid-catalyzed retro-Michael/Michael reactions of acetals **63fb** and **63fc** with EtOH and *n*-PrOH, respectively. Reaction of methylvinyl ketone **13g** with MeOH and EtOH under **2d/56e** catalysis furnished the unexpected tandem hetero-Diels–Alder/acetalization products **64a** and **64b** in good yields rather than the expected oxy-Michael products **63ga** and **63gb** (Table 6, entries 10–11). The stereochemistries of **64a** and **64b** were established based on 2D NMR analysis. Unexpectedly, benzylidene acetone **13a** gave the expected oxy-Michael product **63aa** with very poor conversion and did not furnish the self-Diels–Alder[38] product **65** even after four days (Table 6, entry 12). Hydromethoxylation and hydroethoxylation of cyclohexenone **13h** furnished the expected products **63ha** and **63hb** in moderate yields (Table 6, entries 13–14), however, the reaction of 3-methylcyclohexenone **13i** did not give **63ia** or **63ib**.

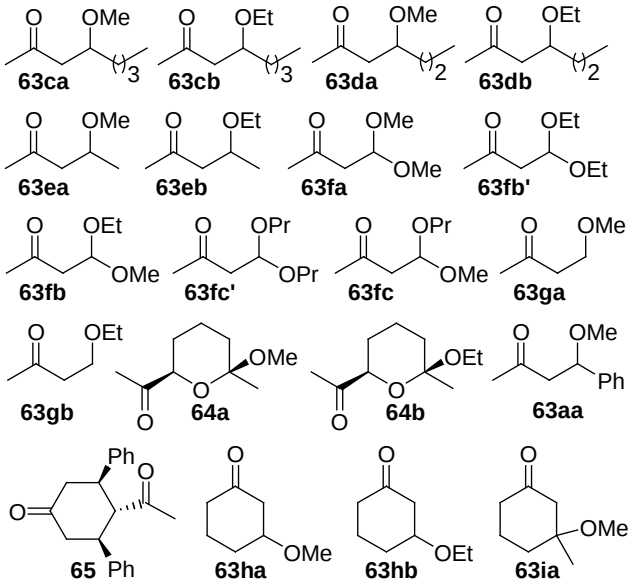
4-Ethoxypentan-2-one **63eb** has been observed in the volatile components of Indian long pepper, *Piper longum Linn*., and also as a volatile metabolite in human urine.[39] Acetals **63fa**, **63fb'** and **63fc'** are useful intermediates in organic synthesis which emphasizes the value of this green approach.

Table 6: Chemically diverse hydroalkoxylated products **63**



Entry	Enone	R^3-OH	Time/h	Product	Yield (%)[a]
1	**13c**	MeOH, **62a**	23	**63ca**	65
2	**13c**	EtOH, **62b**	22	**63cb**	60
3	**13d**	MeOH, **62a**	15	**63da**	75
4	**13d**	EtOH, **62b**	14	**63db**	60
5	**13e**	MeOH, **62a**	17	**63ea**	75
6	**13e**	EtOH, **62b**	18	**63eb**	75
7	**13f**	MeOH, **62a**	28	**63fa**	99
8[b]	**13f**	EtOH, **62b**	30	**63fb, 63fb'**	>95
9[c]	**13f**	^{n}PrOH, **62c**	25	**63fc, 63fc'**	>95
10	**13g**	MeOH, **62a**	3	**63ga**	50
11	**13g**	EtOH, **62b**	3	**63gb**	50
12[d]	**13a**	MeOH, **62a**	96	**63aa**	<5
13	**13h**	MeOH, **62a**	17	**63ha**	55
14	**13h**	EtOH, **62b**	22	**63hb**	55
15[d]	**13i**	MeOH, **62a**	40	**63ia**	–

[a]Yield refers to the column purified product. [b]Ratio **63fb:63fb'** = 1:5.6 as determined by ^{1}H and ^{13}C NMR analysis. [c]Ratio **63fc:63fc'** = 1:5 as determined by ^{1}H and ^{13}C NMR analysis. [d]Enones **13a** and **13i** were recovered.



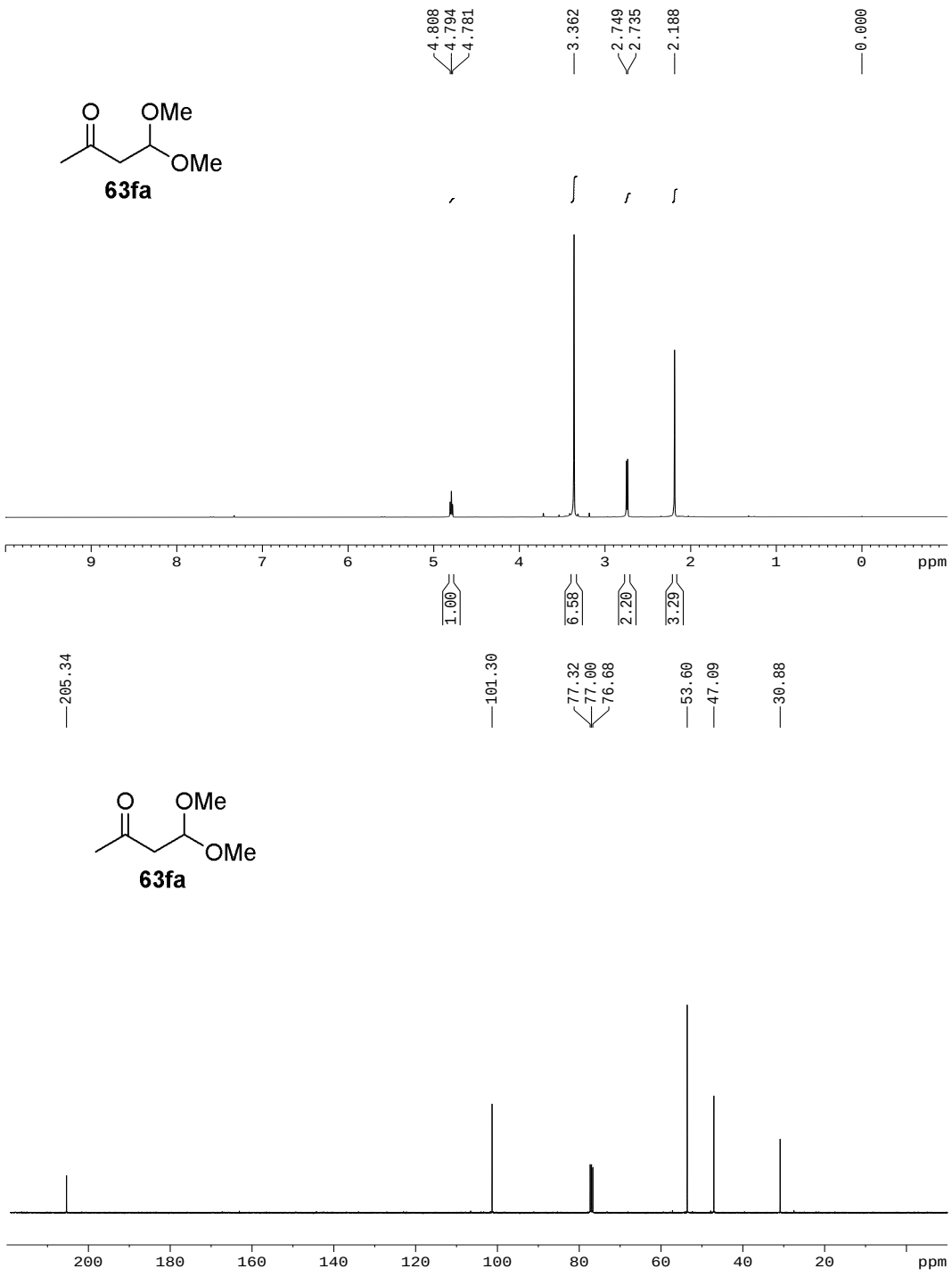


Figure-10: ^{1}H and ^{13}C NMR spectra of the product **63fa**

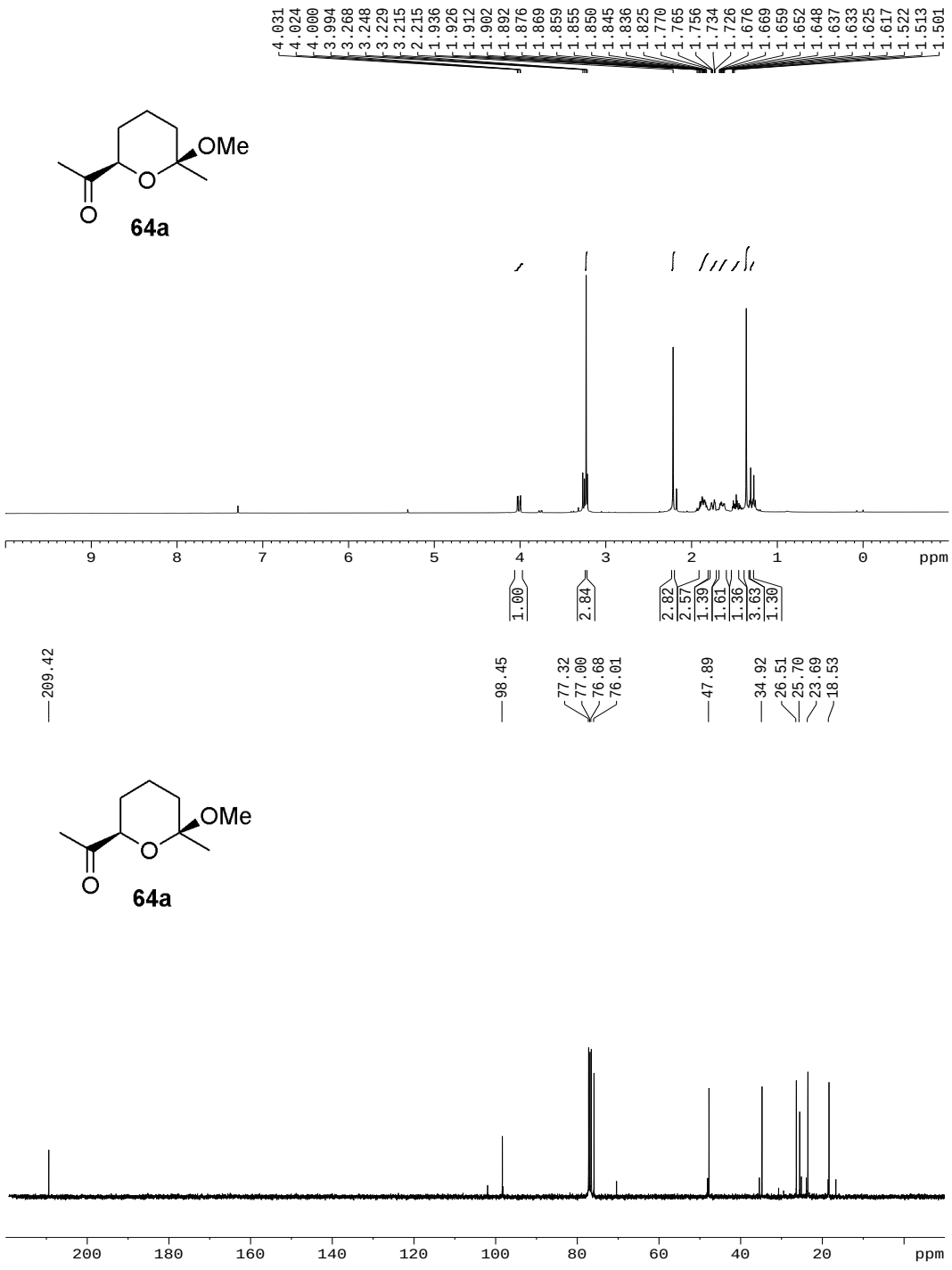
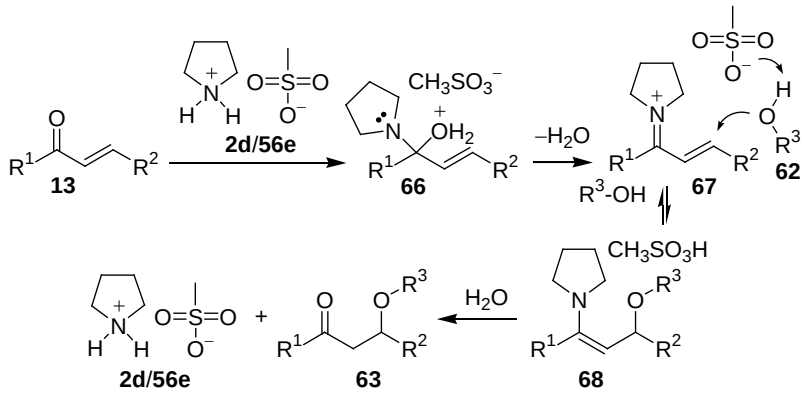


Figure-11: ^{1}H and ^{13}C NMR spectra of the product **64a**

A possible reaction mechanism for the hydroalkoxylation of **13**, **62** and **2a** or **2d/56e** is illustrated in Scheme 6.[37] First, reaction of the amino acid **2a** or amine/acid catalyst **2d/56e** with enone **13** generates the iminium cation **67** (an excellent electrophile) which undergoes a Michael type reaction with *in situ* activated alcohol nucleophiles **62** to generate Michael adduct **68** which is in equilibrium with **67**. Hydrolysis of **68** furnishes the expected oxy-Michael product **63** and free catalyst amino acid **2a** or amine/acid **2d/56e** which is returned to the catalytic cycle. The proposed reaction mechanism was supported by the results presented in Eq. 1 and Table 4, entries 1 and 20.

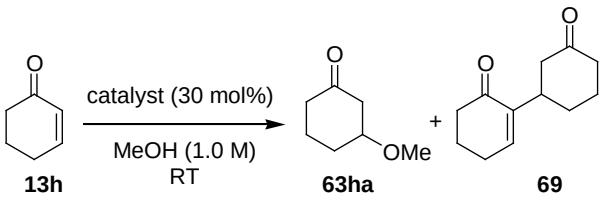
Scheme 6: Proposed reaction mechanism for the organocatalytic hydroalkoxylation of α,β-unsaturated ketones



To understand the role of amine-catalysts **2** on the hydromethoxylation of cyclic enones, the catalysts **2a**, **2d**, **2r** and **2r/56e** were screened for the hydromethoxylation of enone **13h** at room temperature as shown in Table 7. Under proline catalysis, enone **13h** furnished the expected oxy-Michael product **63ha** in 50% yield. Interestingly, amines **2d** and (*S*)-**2r** catalyzed the formation of the unexpected product **69** in good to moderate yields from the enone **13h** and MeOH at room temperature (Table 7, entries 2–3).[40] No reaction was observed by changing the solvent MeOH to THF in the diamine **2r**-catalyzed reaction of enone **13h** and only the starting material was recovered even after four days (Table 7, entry 4). The bifunctional catalyst, **2r/56e** catalyzed the formation of

the hydromethoxylated product **63ha** in good yield from enone **13h** with MeOH (Table 7, entry 5).

Table 7: Direct organocatalytic solvent induced Basavaiah-Baylis-Hillman reaction

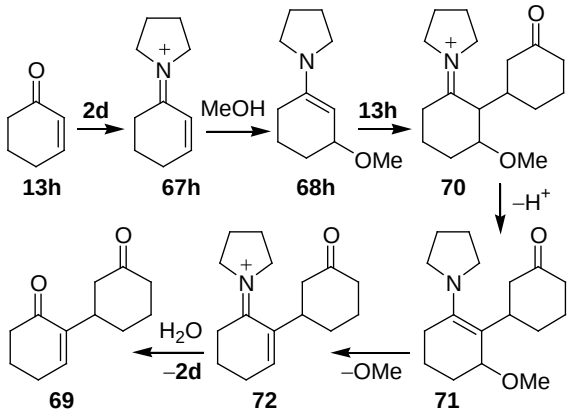


13h **63ha** **69**

Entry	Catalyst	Time/h	Product	Yield[a]
1	**2a**	40	**63ha**	50
2	**2d**	11	**69**	50
3	**2r**	40	**69**	77
4[b]	**2r**	96	**69**	–
5	**2r/56e**	40	**63ha**	65

[a]Yield refers to the column purified product. [b]THF was used as solvent.

Proposed Reaction Mechanism:



Based on the above results, it was proposed that **69** is formed via a solvent induced amine-catalyzed Basavaiah–Baylis–Hillman reaction as shown (see Table 7).[40] Product **69** was shown to possess synergistic herbicidal effects and has been used along with 2,4,5-T and atrazine against Chenopodium album.[41]

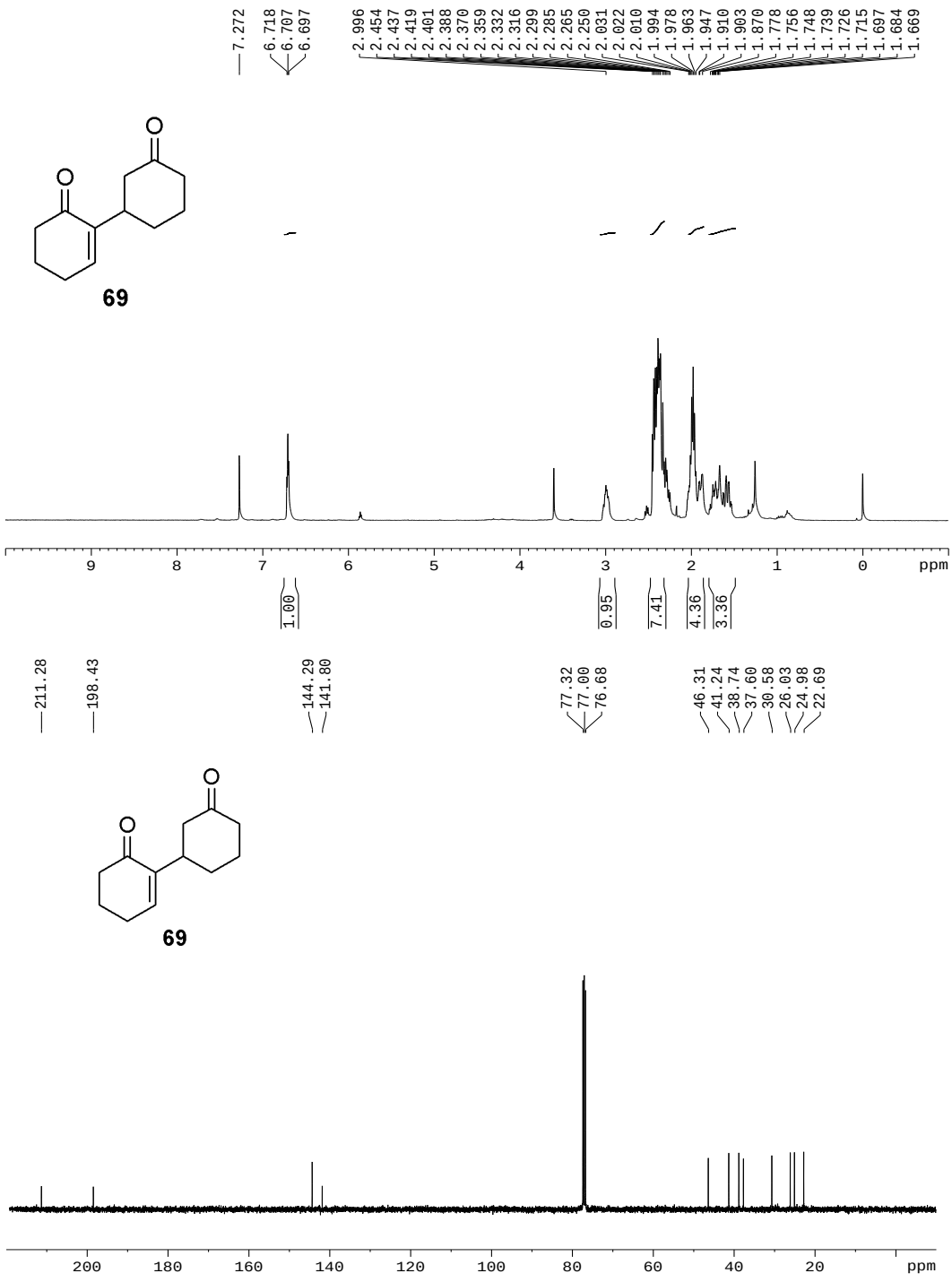


Figure-12: ^{1}H and ^{13}C NMR spectra of the product **69**

4.3 CONCLUSION

In conclusion, it was shown that the mild bifunctional amine/acid **2d/56e** catalyst can be used to catalyze the hydroalkoxylation of α,β-unsaturated systems by an *in situ* iminium activation in the absence of added transition metals. The proposed catalytic cycle suggests that this is a very practical system that could be extended to other classes of bifunctional catalysts to generate active olefins with LUMOs matched to the HOMOs of alcohols. Additionally, the possibility of using other chiral bifunctional amine/acid catalysts would further extend the applicability and practicality of this novel reactivity.

5. A NEW ORGANOCATALYST FOR FRIEDEL-CRAFTS ALKYLATION OF 2-NAPHTHOLS WITH ISATINS: APPLICATION OF AN ORGANO-CLICK STRATEGY FOR THE CASCADE SYNTHESIS OF HIGHLY FUNCTIONALIZED MOLECULES

5.1 INTRODUCTION

Catalytic Friedel-Crafts alkylation is a powerful synthetic method for the preparation of highly functionalized aromatic compounds via C-C and C-N bond formation and consequently can generate important classes of building blocks for pharmaceutically relevant compounds.[42] Due to its atom-economy, the direct catalytic Friedel-Crafts alkylation has received increasing attention.[43] Recently, MacMillan and Jørgensen developed asymmetric Friedel-Crafts alkylation and amination reactions of aromatic molecules with active olefins and electron-deficient substrates using simple chiral amines (organocatalysts) as asymmetric catalysts.[44] Nevertheless, this interesting class of organocatalysts has been used so far only for the following two types of Friedel-Crafts alkylation reactions: (1) the direct Friedel-Crafts alkylation of pyrroles with enals via Michael addition and (2) amination of 2-naphthols with diethyl azodicarboxylates to furnish asymmetric non-biaryl atropisomers.[44]

3-Substituted-3-hydroxyindolin-2-ones are important substrates for studying biological activity as well as useful synthetic intermediates for drug candidates and alkaloids. The 3-substituted-3-hydroxyoxindole moiety is present in several pharmacologically active alkaloids such as celogentin K,[45] donaxaridine,[46] convolutamydines,[47] dioxibrassinine,[48] welwitindolinone C,[49] TMC-95s,[50] and 3′-hydroxyglucoisatisin,[51] in addition to several others. As a consequence, the development of practical methods for their preparation is of interest. Again the

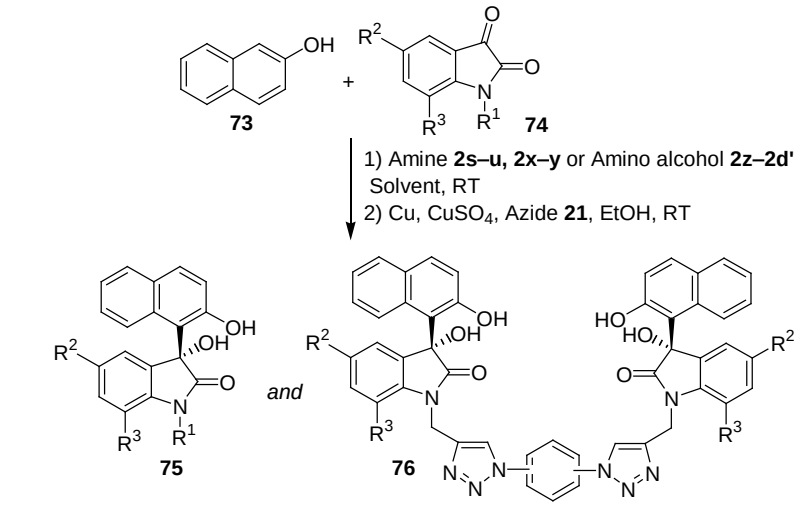
development of new carbon-carbon bond-forming reactions under mild and greener conditions is one of the main objectives in organic synthesis. These requirements provided the necessary activation to develop a new organo-catalytic Friedel-Crafts alkylation of 2-naphthols **73** with substituted isatins **74** to furnish 3-substituted-3-hydroxyindolin-2-ones **75** (Scheme 7).

Chiral dialkylamino-ethanol derivatives (e.g., cinchona alkaloids) have been catalysts of choice for the activation of CH-acids and alcohols, leading to a number of asymmetric additions of various nucleophiles to electron-deficient substrates.[52] These dialkylamino-ethanol derivatives **2z-2c'** were utilized as catalysts for the Friedel-Crafts alkylation of 2-naphthols **73** with substituted isatins **74** to furnish highly functionalized 3-aryl-3-hydroxyindolin-2-ones **75** in good yields as shown in Scheme 7. The development of organo-click,[53] three-component Friedel-Crafts alkylation/Huisgen cycloaddition (FCA/HC) reactions which produce highly functionalized 1,2,3-triazoles **76** from 2-naphthol **73**, 1-prop-2-ynyl-1*H*-indole-2,3-dione **74l**, benzyl azide **21a** or bis-azido benzenes **21b-d**, catalyst **2c'**, copper and copper sulfate is described in the following sections.

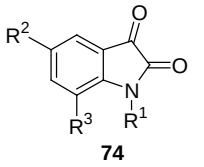
The mechanistic proposal for the Lewis base-catalyzed Friedel-Crafts reaction of 2-naphthol **73** with isatins **74** in aprotic-nonpolar and protic-polar solvents indicates the involvement of **TS-1** and **TS-2**, respectively (Scheme 7). Interestingly, combination of a domino Lewis base and Brønsted acid-catalyzed Friedel-Crafts reaction of 2-naphthol **73** with isatins **74** in aprotic-nonpolar solvents indicates that **TS-3** is involved in the reaction. Thus, it was speculated that simple dimethylamino-ethanol **2c'** was potentially capable of promoting the direct Friedel-Crafts reaction via **TS-3**.

Herein, this new dimethylamino-ethanol **2c'** catalyzed Friedel-Crafts alkylation of 2-naphthols **73** with substituted isatins **74** to furnish highly functionalized 3-aryl-3-hydroxyindolin-2-ones **75** is presented.

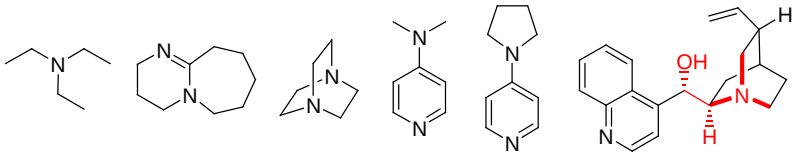
***Scheme 7*:** Direct application of an organo-click strategy for the cascade synthesis of highly functionalized molecules

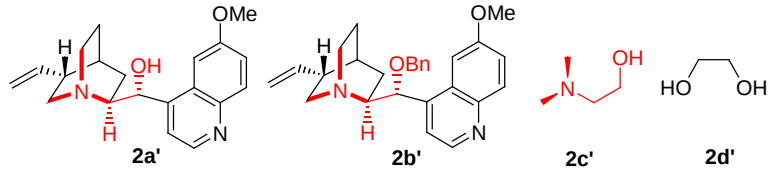


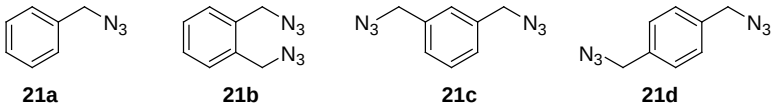
Substrates and Catalysts Screened:

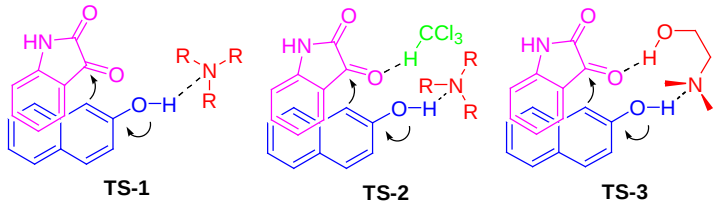


74a: $R^1 = R^2 = R^3 = H$; **74b:** $R^1 = Me$, $R^2 = R^3 = H$
74c: $R^1 = H$, $R^2 = R^3 = Me$; **74d:** $R^1 = R^3 = H$, $R^2 = F$
74e: $R^1 = R^3 = H$, $R^2 = Cl$; **74f:** $R^1 = R^3 = H$, $R^2 = Br$
74g: $R^1 = R^3 = H$, $R^2 = I$; **74h:** $R^1 = R^3 = H$, $R^2 = NO_2$
74i: $R^2 = R^3 = H$, $R^1 = CH_2CH_3$; **74j:** $R^2 = R^3 = H$, $R^1 = CH_2Ph$
74k: $R^2 = R^3 = H$, $R^1 = CH_2CH{=}CH_2$; **74l:** $R^2 = R^3 = H$, $R^1 = CH_2CCH$









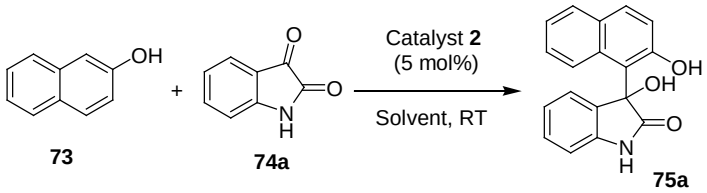
5.2 RESULTS AND DISCUSSIONS

The preliminary Friedel-Crafts alkylation (FCA) reaction between 2-naphthol **73** and isatin **74a** was carried out with 10 mol% of TEA **2u** as catalyst in $PhCH_3$. As expected, the reaction afforded product **75a** in 99% conversion and 90% yield after 24 h via **TS-1** (Table 8, entry 1), which was purified by simple filtration followed by column chromatography. The rate of the **2u**-catalyzed FCA reaction was increased in $CHCl_3$ and CH_2Cl_2 (entries 2 and 3). DBU **2s** did not catalyze the FCA reaction, however DABCO **2t** catalyzed the FCA reaction with 70% conversion after 24 h in $PhCH_3$ (entries 4 and 5). DMAP **2x** and 4-pyrrolidin-1-yl-pyridine **2y** catalyzed the FCA reaction of **73** and **74a** to furnish the expected product **75a** in 80% and 99% conversions after 24 h and 10 h, respectively, in $PhCH_3$ (entries 6 and 7). Interestingly, the cinchona alkaloids, cinchonine **2z** and quinine **2a'** catalyzed the FCA reaction in $PhCH_3$ to furnish **75a** with 99% conversion after 6–8 h as shown in entries 8 and 9, Table 8. Unfortunately only <10% *ee* was observed in the cinchona alkaloids, cinchonine **2z** and quinine **2a'**, catalyzed FCA reactions of **73** and **74a** in $PhCH_3$ or CH_2Cl_2. This unexpected, rapid FCA reaction with cinchonine **2z** and quinine **2a'** can be explained by the involvement of both the amine and alcohol groups of **2z** and **2a'** in the transition state. This was further confirmed by testing the FCA reaction of **73** and **74a** with alcohol protected quinine **2b'**, which required a longer reaction time to furnish the FCA product **75a** in $PhCH_3$ with 70% conversion (Table 8, entry 10).

Next, the same reaction was studied employing active dimethylamino-ethanol **2c'** as catalyst (see Scheme 7). Interestingly, FCA reactions of **73** and **74a** with 5 mol% of **2c'** in $PhCH_3$, PhH or CH_2Cl_2 at 25 °C for 3–5 h furnished the expected FCA adduct **75a** in 99% conversion and 96% yield (Table 8, entries 11–13). Dimethylamino-ethanol **2c'** catalyzed the FCA reaction through **TS-3** as depicted in Scheme 7 and this was further confirmed by controlled experiments (Table 8, entries 14–17). The optimum

conditions (entries 11 and 13) involved the usage of 5 mol% of catalyst **2c'** in $PhCH_3$ or CH_2Cl_2 at 25 °C.

***Table 8*:** Optimization of the organocatalytic Friedel-Crafts alkylation of 2-naphthol **73** with isatin **74a**



73 **74a** **75a**

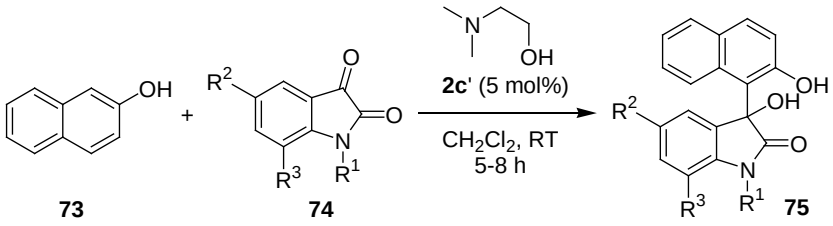
Entry	Catalyst	Solvent	Time/h	Conversion (%)[a]	Yield (%)[b]
1[c]	**2u**	$PhCH_3$	24	99	90
2[c]	**2u**	$CHCl_3$	9	99	92
3[c]	**2u**	CH_2Cl_2	9	99	90
4	**2s**	$PhCH_3$	24	–	–
5	**2t**	$PhCH_3$	24	70	60
6	**2x**	$PhCH_3$	24	80	75
7	**2y**	$PhCH_3$	10	99	96
8	**2z**	$PhCH_3$	6	99	97
9	**2a'**	$PhCH_3$	8	99	94
10	**2b'**	$PhCH_3$	24	70	60
11	**2c'**	$PhCH_3$	5	99	96
12	**2c'**	PhH	3	99	96
13	**2c'**	CH_2Cl_2	5	99	96
14	**2c'**	DMSO	24	20	10
15	**2d'**	$PhCH_3$	24	5	<5
16	**2u/2d'**	$PhCH_3$	8	99	96
17	**–**	$PhCH_3$	24	5	<5

[a]Both reactants **73** and **74a** and catalyst **2** were mixed at the same time in solvent and stirred at room temperature; conversion based on TLC and ^{1}H NMR analysis. [b]Yield refers to the column purified product. [c]10 mol% of triethyl-amine **2u** was used as catalyst.

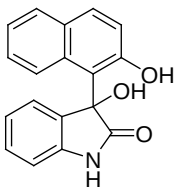
After these interesting results, the scope and limitations of the FCA reaction with a range of isatins **74a–l** using 5 mol% of **2c'** as catalyst in CH_2Cl_2 at 25 °C was

investigated (Table 9). Different 5-substituted isatins **74c–h** and 1-substituted isatins **74b**, **74i–l** furnished adducts **75a–l** in very good yields. Many of the products were purified by simple filtration to give 90–95% purity.

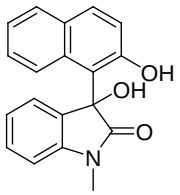
***Table 9*:** Chemically diverse libraries of Friedel-Crafts alkylation products **75**[a]



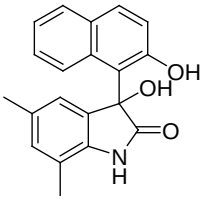
73 **74** **75**



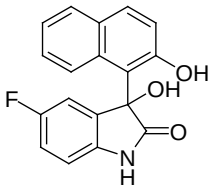
96**% (75a)**



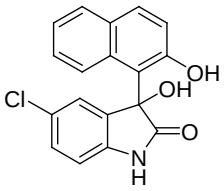
89**% (75b)**



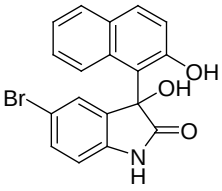
89**% (75c)**



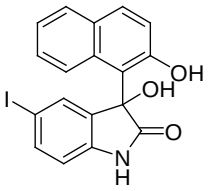
94**% (75d)**



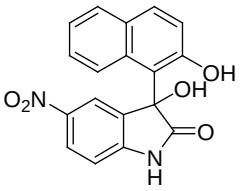
93**% (75e)**



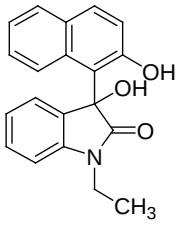
92**% (75f)**



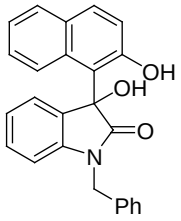
92**% (75g)**



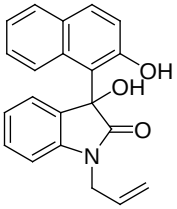
92**% (75h)**



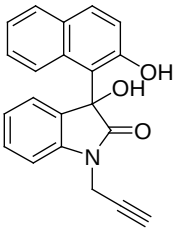
91**% (75i)**



92**% (75j)**



94**% (75k)**



92**% (75l)**

[a] Yield refers to the column purified product.

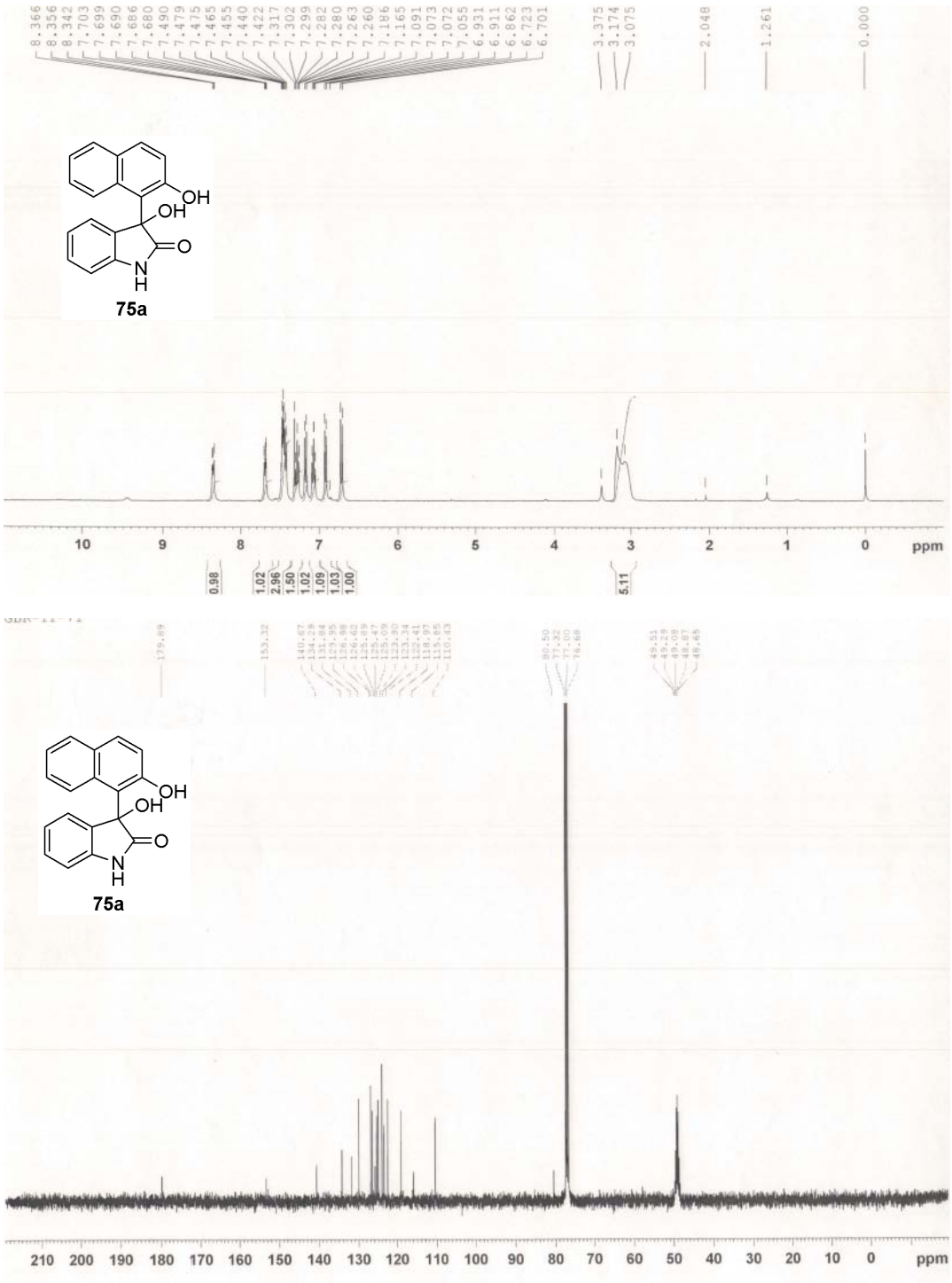


Figure-13: ^{1}H and ^{13}C NMR spectra of the product **75a**

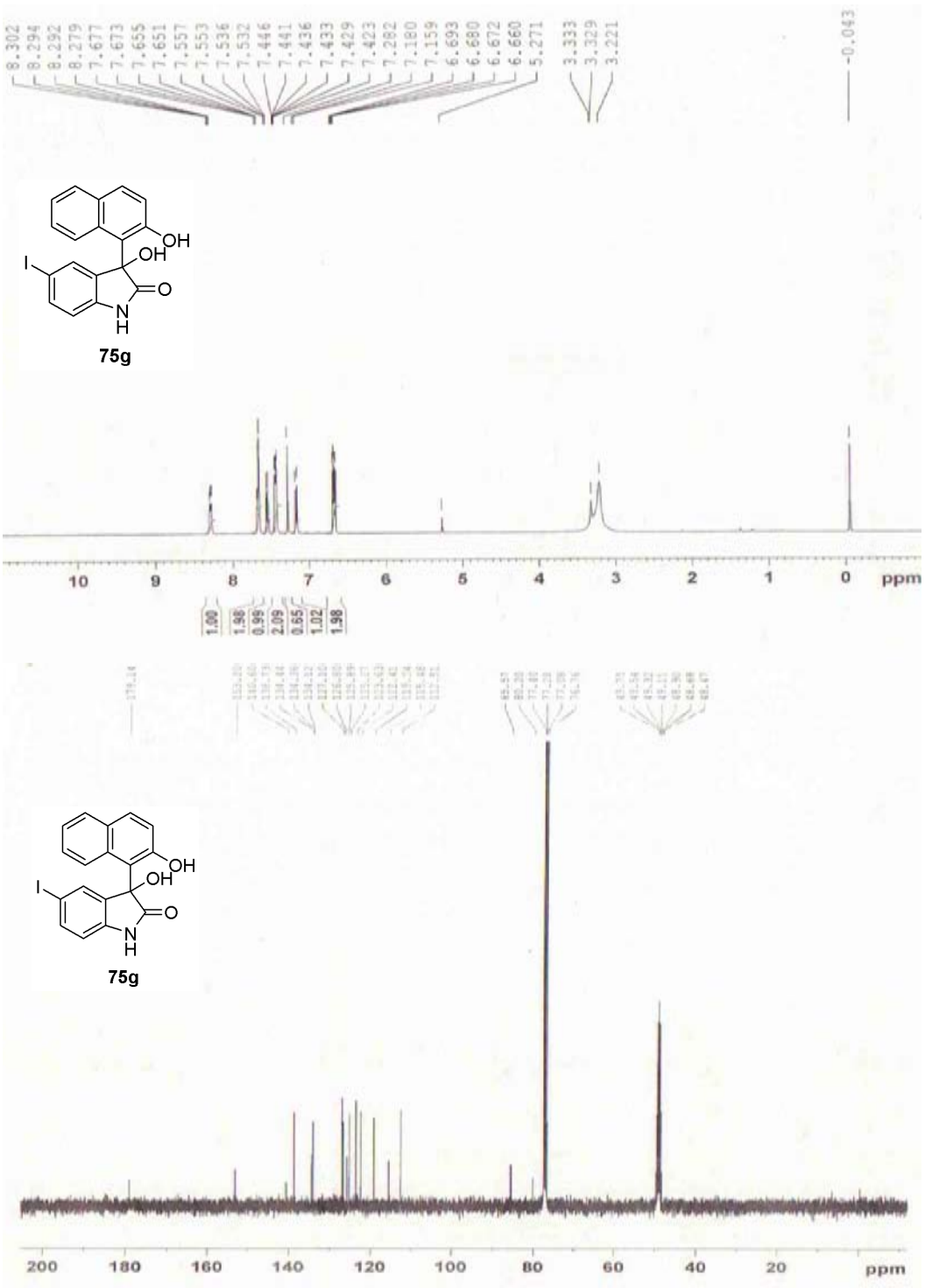
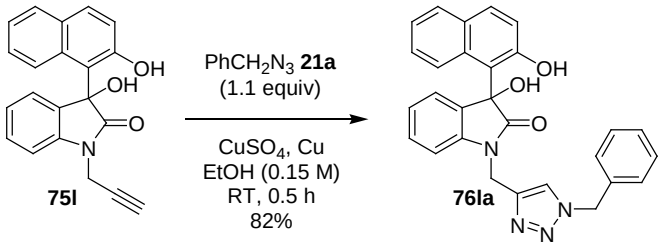


Figure-14: ^{1}H and ^{13}C NMR spectra of the product **75g**

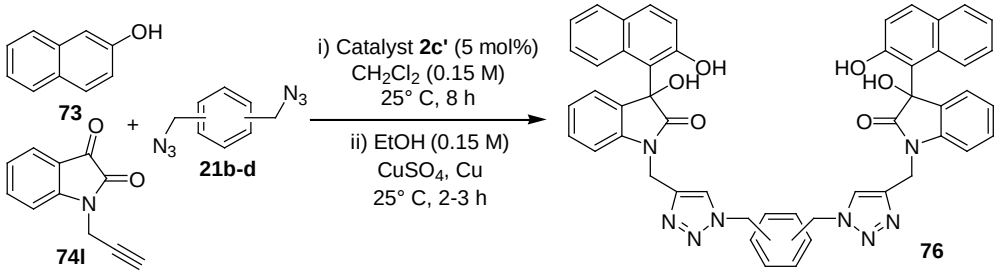
Huisgen 1,3-dipolar cycloadditions[54] are important processes. The cycloaddition of azide and alkyne furnishes triazole which is a very useful member of this family. Huisgen cycloaddition of propargyl substituted, 3-hydroxy-3-(2-hydroxy-naphthalen-1-yl)-1-prop-2-ynyl-1,3-dihydroindol-2-one **75l** with benzyl azide **21a** under $CuSO_4$/Cu catalysis furnished 1,4-disubstituted [1,2,3]-triazole **76la**, regioselectively in one-pot in very good yield (Scheme 8). [1,2,3]-Triazole **76la** was furnished in the same yield via both two and three-component strategies. [1,2,3]-Triazoles have found wide applications in biology, chemistry, and materials science,[55] thus new approaches to diverse products are important.

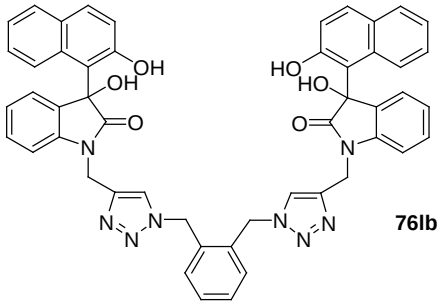
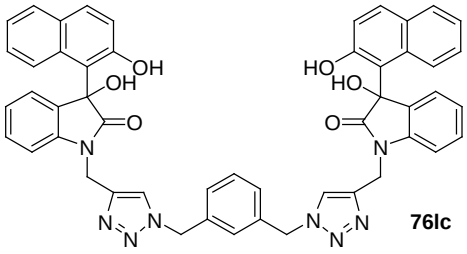
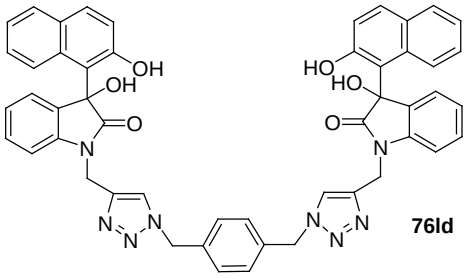
***Scheme 8*:** Organo/Cu^I-catalyzed synthesis of highly substituted 1, 2, 3-triazole in one-pot



It was interesting to find that **75l** also reacted with 1,2-bis-azidomethyl-benzene **21b** in EtOH under $CuSO_4$/Cu-catalysis to furnish the expected di-[1,2,3]-triazole **76lb** in 76% yield with formation of one new carbon-carbon σ bond and four new carbon-nitrogen σ bonds in one-pot (Table 10, entry 1). Regiochemistry of the organo-click products **76** were established as 1,4-disubstituted-1,2,3-triazole based on correlation with previous experiments (see ref. 45 and 54). The scope of this dimethylamino-ethanol/Cu^I-catalyzed synthesis of compounds of type **76** is revealed by the examples in Table 10.

***Table 10*:** Organo/Cu^{I}-catalyzed stereospecific synthesis of polysubstituted triazoles via Friedel-Crafts alkylation/Huisgen cycloaddition reactions in one-pot



Entry	Product	Yield (%)[a]
1	 **76lb**	76
2	 **76lc**	80
3	 **76ld**	81

[a]Yield refers to the column purified product.

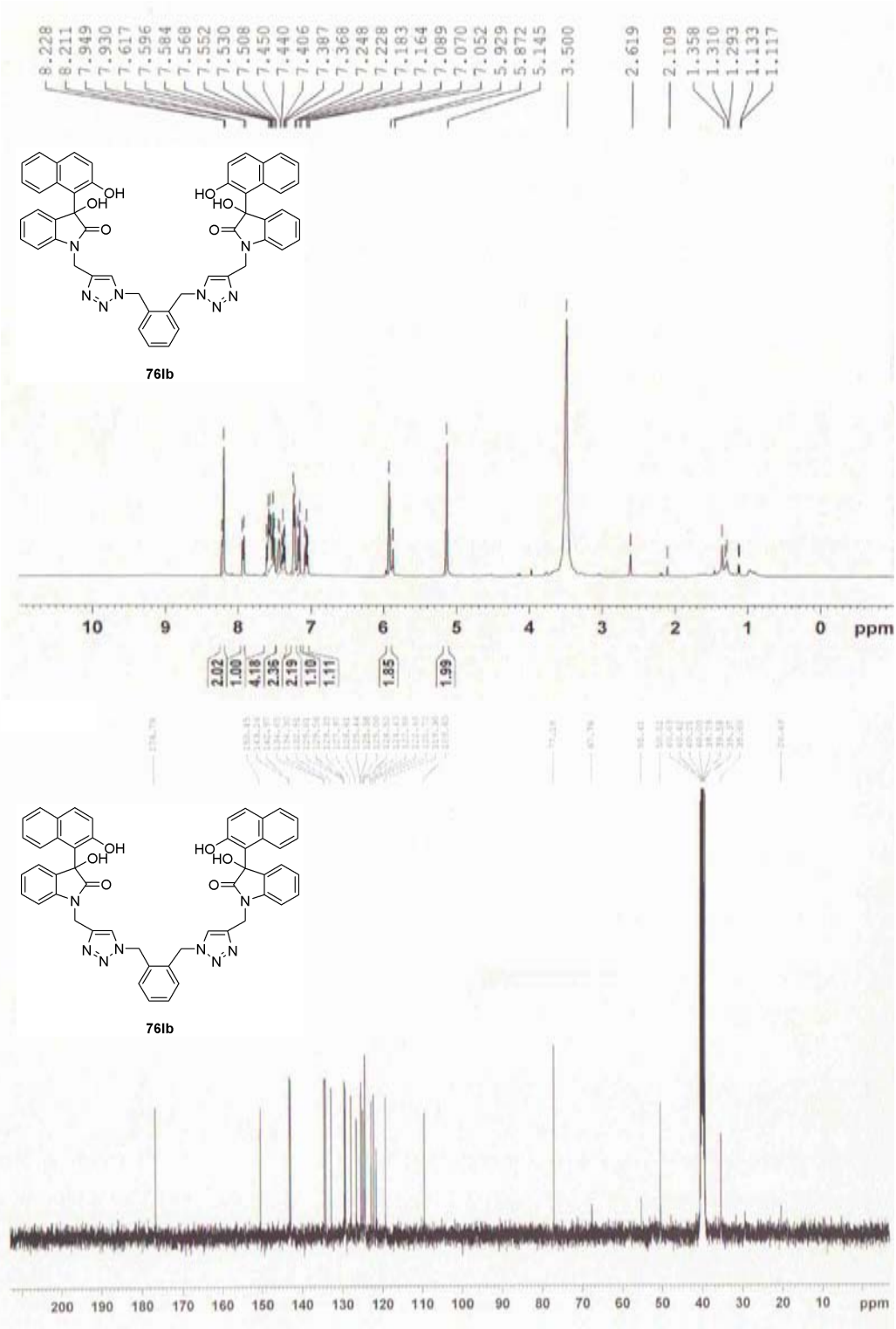


Figure-15: ^{1}H and ^{13}C NMR spectra of the product **76lb**

5.3 CONCLUSION

In summary, a novel dimethylamino-ethanol catalyzed FCA reaction and dimethylamino-ethanol/Cu^{I}-catalyzed cascade FCA/Huisgen cycloaddition reactions through formation of one C-C and four C-N bonds in a single step, was developed. This experimentally simple approach can be used to construct highly substituted 3-aryl-3-hydroxyindolin-2-ones **75** and 1,4-disubstituted [1,2,3]-triazoles **76** in a regioselective fashion with very good yields. The possibility of using chiral dialkylamino-ethanol derivatives as catalysts could extend the scope of this reaction to an asymmetric variant.

6. RAPID SYNTHESIS OF FUNCTIONALISED INDENES, TRIAZOLES AND GLUCOCORTICOID RECEPTOR MODULATORS BY SEQUENTIAL MULTICATALYTIC CASCADE REACTIONS

6.1 INTRODUCTION

Functionalized indenes and 1,2,3-triazoles are important classes of carbo- and heterocycles. They exist as basic skeletons in a wide variety of biologically active compounds and are used as drug intermediates in pharmaceuticals (Figure-16).[56] As such, the development of new and more general catalytic methods for their preparation is of significant interest.[57] On the other hand synthesis of highly functionalized molecules via "combination of multi-component reactions (MCR) and multi-catalysis cascade (MCC) reactions" has become a trend in modern synthetic organic chemistry.[58] Hence, a one-pot synthesis of indenes and 1,2,3-triazoles involving the MCC strategy from common substrate and catalyst would be an important task to be accomplished.

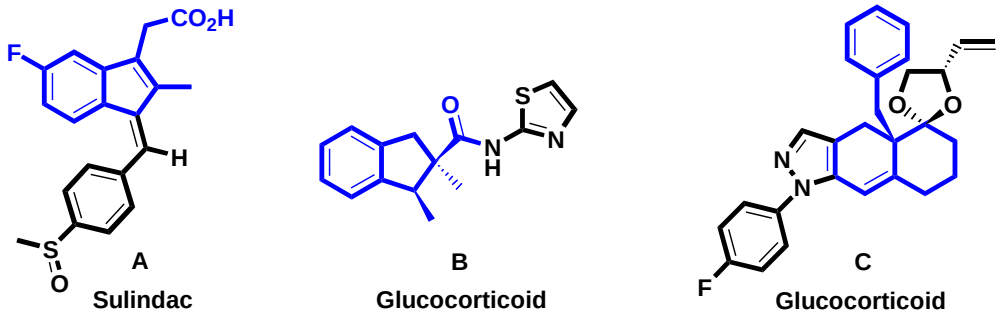


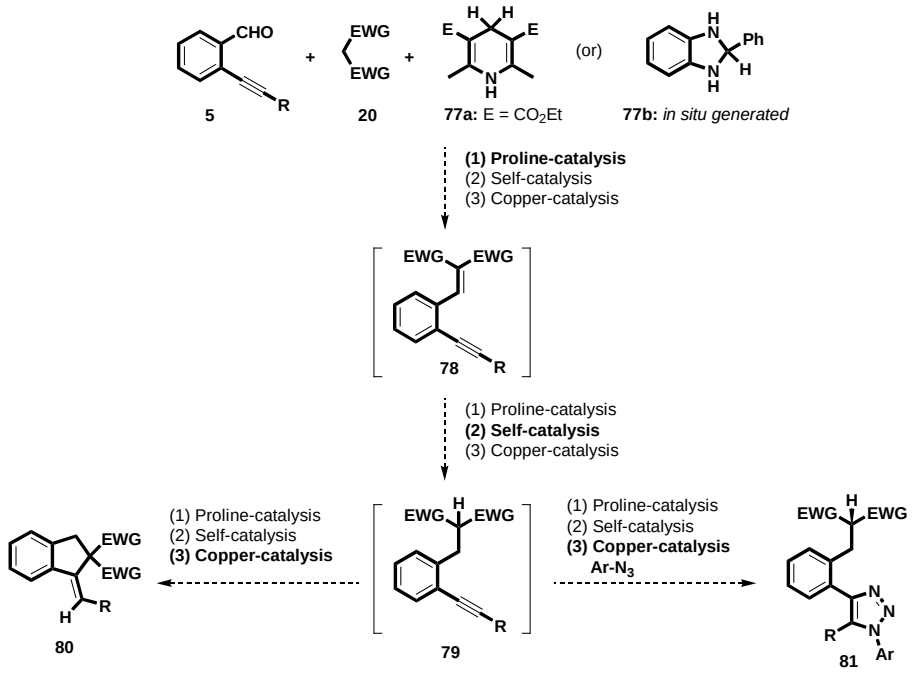
Figure-16: Biologically important compounds containing indene and 1,2,3-triazole backbone

Transition metal catalyzed cascade reactions is a vastly growing field. The addition of active nucleophiles to alkyne functionality under coinage metal catalysis

(Cu, Ag and Au), has received remarkable attention over the past decade and is under continuous development.[59] Particularly, soft coinage metal ions have been shown to be highly potent in activating alkyne functionality and thus can trigger a cascade process.[59]

Combination of amino acid and suitably ligated coinage metal ion complexes could be identified as multi-catalysts and that will be ideal synthetic strategy compared to cellular reactions.[59a] Combining iminium activation of aldehydes, self activation of olefins and simultaneous metal ion activation of alkynes in a cascade sequence could constitute a new carbocyclization (CC) method and heterocyclization (HC) method to furnish indenes through Conia-ene reaction[60] and 1,2,3-triazoles *via* [3+2]-cycloaddition reaction respectively, from common substrate and catalyst as shown in Scheme 9. Herein, the findings regarding these new MCC reactions and application to the high-yielding synthesis of glucocorticoid receptor modulators are disclosed.

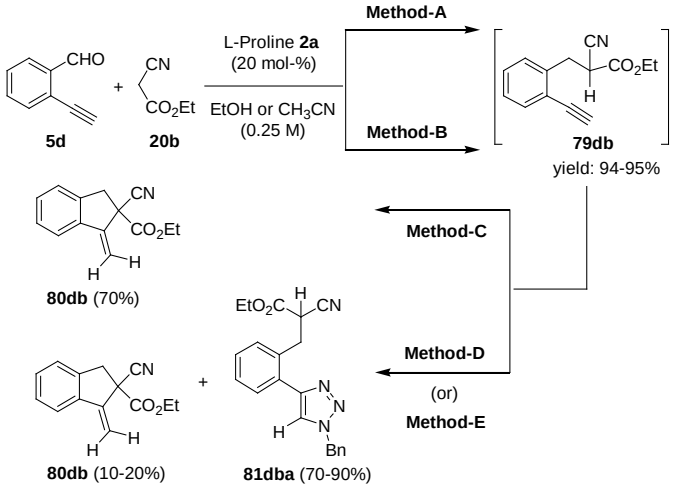
Scheme 9: MCC approach to functionalized indenes and triazoles



6.2 RESULTS AND DISSCUSSION

MCC studies were initiated by optimizing an olefination, hydrogenation, and cyclization sequence of **5d**, **20b**, **77a**/**77b** and BnN_3 **21a** by using different conditions and some representative results are shown in Scheme 10. L-proline was found to readily catalyze the olefination of **5d** with **20b** to furnish active olefin **78db** which upon *in situ* treatment with Hantzsch ester **77a** produced hydrogenated product **79db** with very good yield in EtOH, *t*-BuOH, or CH_3CN at 25 °C for 24 h. The same reaction with *in situ* generated 2-phenyl-2,3-dihydro-1*H*-benzoimidazole **77b** also furnished product **79db** with 95% yield in protic solvents. The optimum conditions involved the usage of 20 mol% catalyst in cascade olefination/hydrogenation reaction of **5d**, **20b** and **77a**/**77b** in EtOH, *t*-BuOH, or CH_3CN at 25 °C to furnish **79db** in very good yield (see Scheme 10). After the successful synthesis of **79db**, different conditions were investigated for the carbocyclization of **79db** in one-pot as shown in Scheme 10 and Table A1. Interestingly, reaction of **79db** under the optimized conditions (15 mol% of L-proline, 10 mol% of CuI, and 2 equiv. of Cs_2CO_3) in CH_3CN at 25 °C for 0.5 h furnished indene **80db** in 90% yield (Table A1). Sequential one-pot combination of L-proline-/self-catalyzed olefination/hydrogenation reaction and CuI/L-proline/Cs_2CO_3-catalyzed carbocyclization of **5d**, **20b** and **77a** in CH_3CN at 25 °C for 26 h furnished indene **80db** with slightly reduced yield as shown in Scheme 10. The MCC reaction of **5d**, **20b** and **77a** in CH_3CN at 25 °C for 2.5–12.5 h under the combination of pyrrolidine or morpholine with CuI/Cs_2CO_3 catalysis also furnished indene **80db** in 64–70% yield (Schemes. A1 and A2). Interestingly, reaction of **79db** with CuI/L-proline /DIPEA in CH_3CN at 25 °C for 14 h furnished indene **80db** in 86% yield, but there was no reaction with $CuSO_4$/Na–(+)-ascorbate in *t*-BuOH and H_2O at 25 °C for 20 h as shown in Table A1, entries 15–17.

Scheme 10: Optimization of the carbocyclization and heterocyclization reactions



Method A: Compound **20b** (0.5 mmol), **5d** (0.5 mmol), **77a** (0.5 mmol), L-proline (20 mol%, 0.1 mmol); EtOH or *t*-BuOH or CH_3CN (0.25 M); 25 ^{o}C, 24 h. **Method B**: Compound **20b** (0.5 mmol), **5d** (0.5 mmol), L-proline (20 mol%, 0.1 mmol); EtOH (0.25 M); 25 ^{o}C, 0.5 h; then, **82** (0.5 mmol), PhCHO (0.5 mmol), 25 ^{o}C, 12 h. **Method C**: Compound **79db**, CuI (0.05 mmol, 10 mol%, 9.5 mg), Cs_2CO_3 (1 mmol, 2 equiv., 326 mg),CH_3CN (1.0 ml); 25 ^{o}C, 2 h. **Method D**: Compound **79db**, BnN_3 **21a** (1.0 mmol, 2 equiv.), CuI (0.05 mmol, 10 mol%, 9.5 mg), DIPEA (30 mol%),CH_3CN (1.0 ml); 25 ^{o}C, 6 h. **Method E**: Compound **79db**, BnN_3 **21a** (0.6 mmol, 1.2 equiv.), $CuSO_4.5H_2O$ (0.1 mmol, 20 mol%, 25 mg), Na-(+)-ascorbate (0.2 mmol, 40 mol%, 40 mg), H_2O (1.0 ml), *t*-BuOH (1.0 ml); 25 ^{o}C, 3 h**.**

After testing the sequential one-pot olefination/hydrogenation and carbocyclization reaction of **5d**, **20b** and **77a** under L-proline/CuI/base catalyses, further investigation was carried out on the intermolecular [3+2] cycloaddition of olefination/hydrogenation product **79db** with BnN_3 **21a** to furnish 1,2,3-triazole **81dba** in one-pot under the same catalytic conditions as shown in Scheme 10. Interestingly, the sequential one-pot reaction of *in situ* generated **79db** with BnN_3 **21a** (2 equiv.) under the optimized conditions (15 mol% of L-proline, 10 mol% of CuI, 30 mol% of DIPEA) in CH_3CN at 25 °C for 6 h furnished 1,2,3-triazole **81dba** in 70% yield and indene **80db** in 20% yield (Scheme 10). In a similar manner, sequential one-pot combination of L-proline/self-catalyzed olefination/hydrogenation reaction and $CuSO_4$/Na–(+)-ascorbate-catalyzed heterocyclization of **5d**, **20b**, **77a** and BnN_3 **21a** in *t*-BuOH and H_2O at 25 °C for 27 h furnished 1,2,3-triazole **81dba** in 90% yield and indene **80db** in 10% yield (Scheme 10).

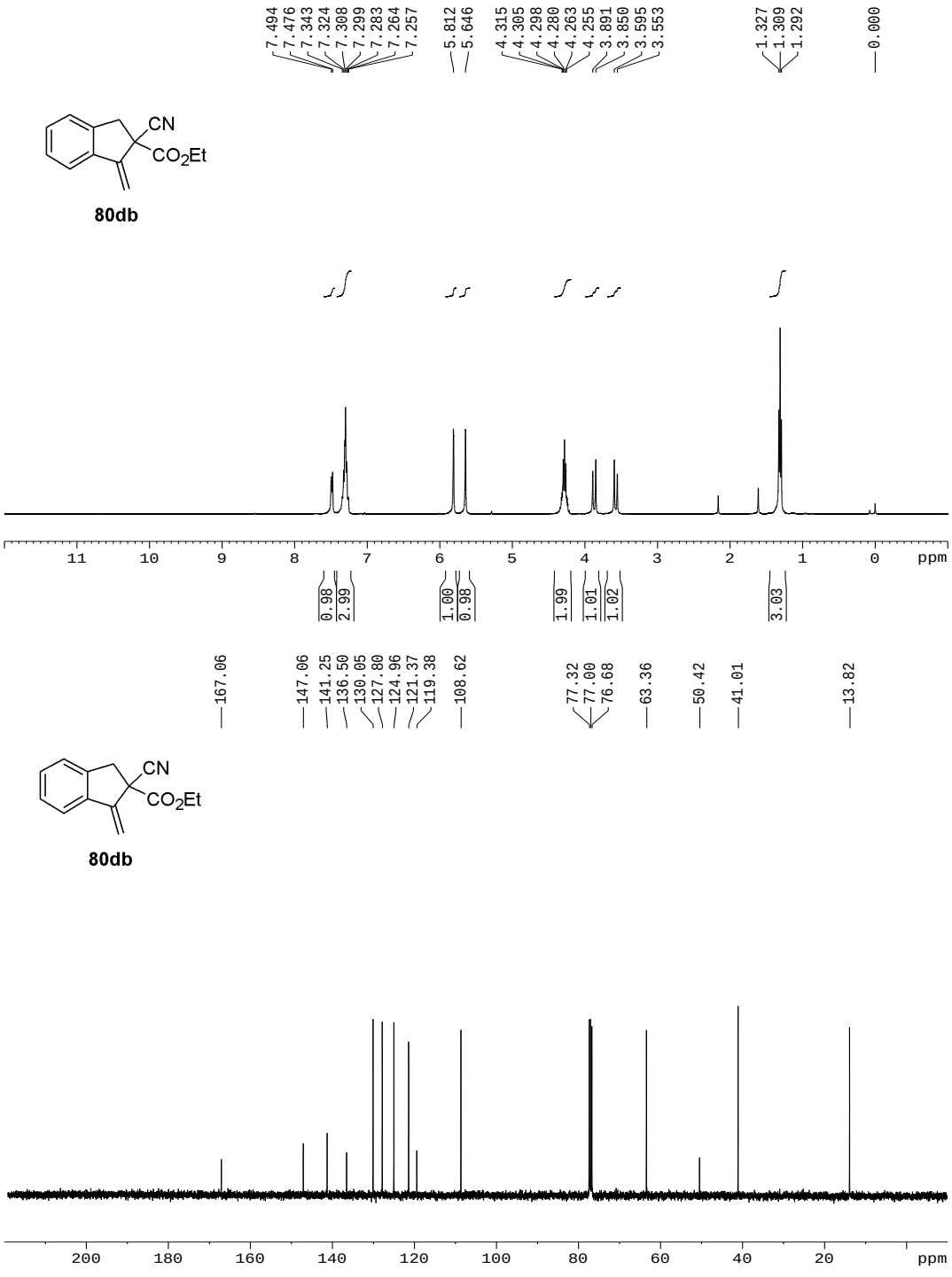


Figure-17: ^{1}H and ^{13}C NMR spectra of the product **80db**

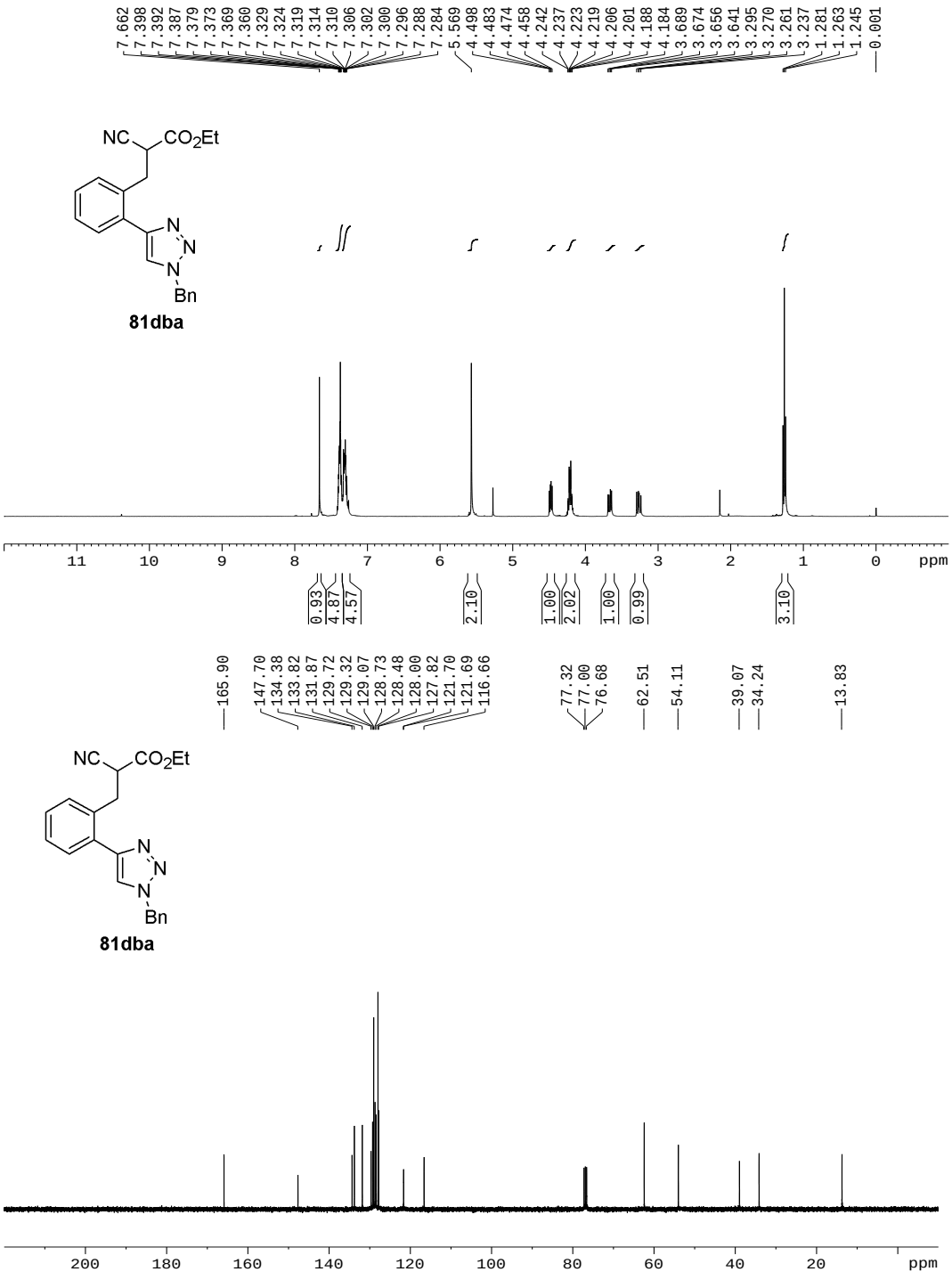


Figure-18: ^{1}H and ^{13}C NMR spectra of the product **81dba**

With the optimized reaction conditions, the scope of the MCC reactions was investigated. A variety of CH acids **20a–m** were treated with **5d** (1 equiv.) and **77a** (1 equiv.) under sequential catalysis of L-proline (5 to 20 mol%) and CuI/Cs_2CO_3 or CuI/Et_3N in CH_3CN at 25 °C for 0.5 to 2 h (Table 11). Acyclic and cyclic CH acids **20a–m** generated the expected Conia-ene products **80** with excellent yields (Table 11). Reaction of a menthol derivative of CH acid **20e** with **5d** and **77a** under L-proline/CuI/Cs_2CO_3 catalysis furnished (–)-**80de**, but unfortunately only 20% *de* was observed (Table 11). Interestingly, reaction of cyclic CH acids **20a, 20g–i** with **5d** and **77a** under L-proline/CuI catalyses and the reaction of CH acids **20j–m** with **5d** and **77a** under L-proline/CuI/Et_3N catalyses furnished the monospiro and dispiro compounds **80da**, **80dg–dm** as major products in 70–95% yields, which are sesquiterpenoid analogues (Table 11). Possibly due to the highly acidic nature of cyclic CH acids **20a**, **20g–m** compared to acyclic CH acids **20b–f**, the Conia-ene reaction for compounds **79da**, **79dg–dm**, under L-proline/CuI or L-proline/CuI/Et_3N catalysis, proceeded in absence of a strong base, as shown in Table 11.

The structure of the products **80da–dm** were determined by NMR spectroscopic analysis and also finally confirmed by X-ray structure analysis of **80dh** (Figure-19).[61]

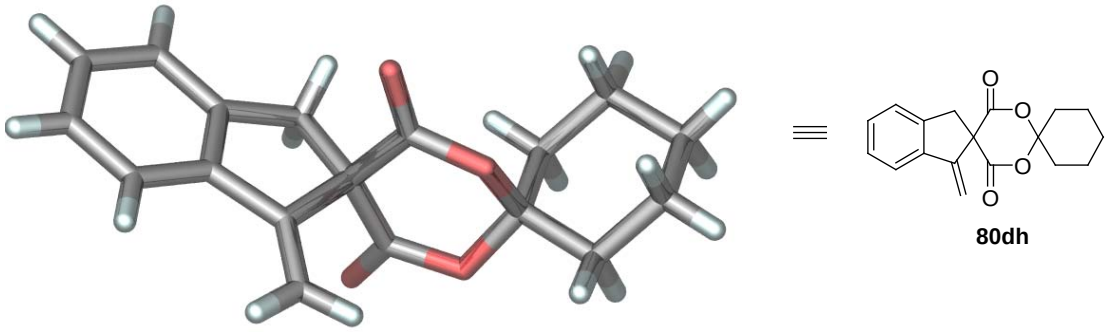
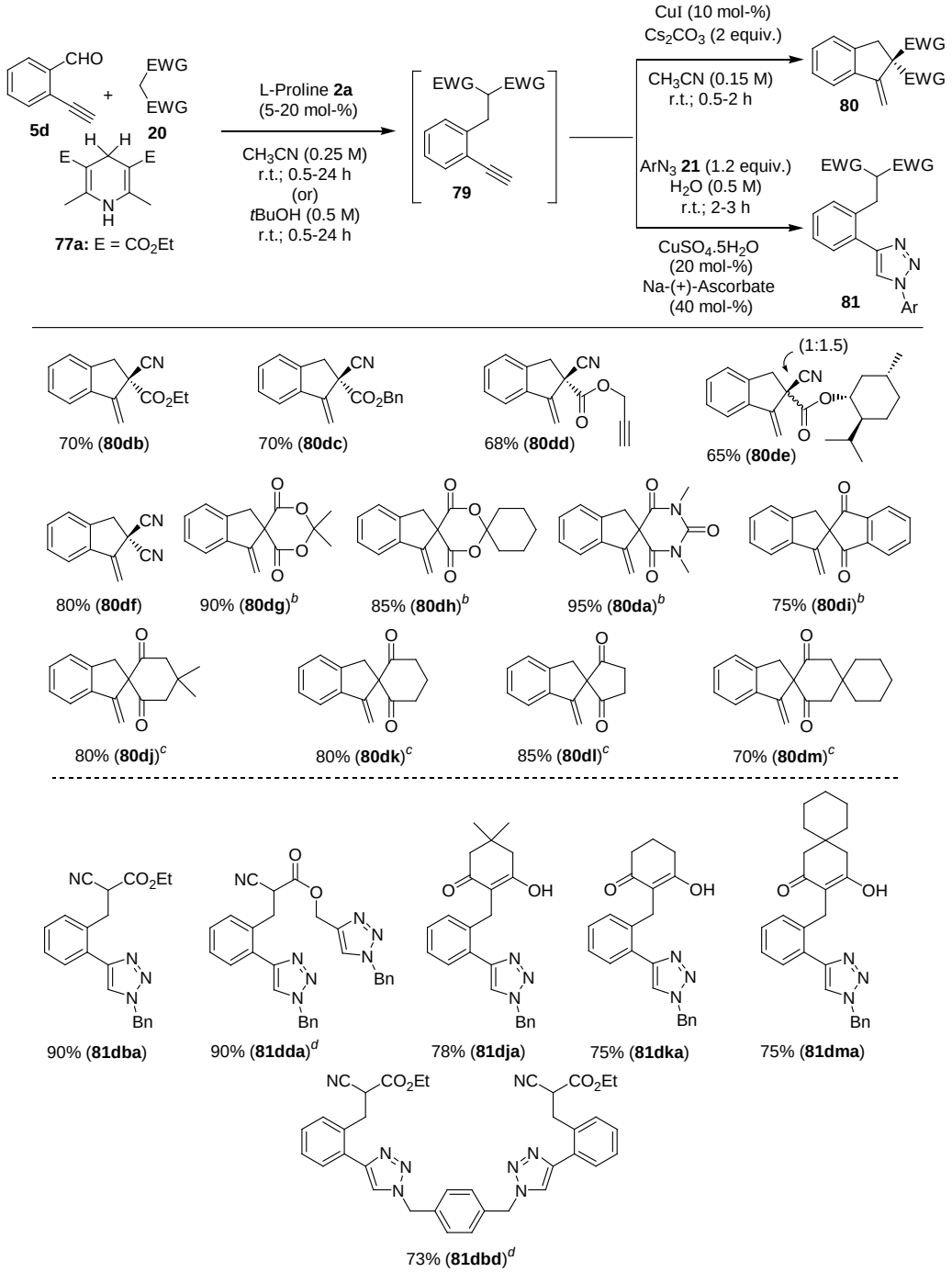


Figure-19: Crystal structure of 1’’-methylenedispiro[cyclohexane-1,2’-(dihydro-4’*H*-[1,3]dioxane)-5’,2’’-(2’’,3’’-dihydro-1’’*H*-indene)]-4’,6’-dione (**80dh**)

Table 11: One-pot synthesis of indene and 1,2,3-triazole products[a]



[a]Yield refers to the column-purified products. [b]Cs_2CO_3 was not used. [c]Et_3N (30 mol%) was used instead of Cs_2CO_3. [d]Reaction time was 12 h.

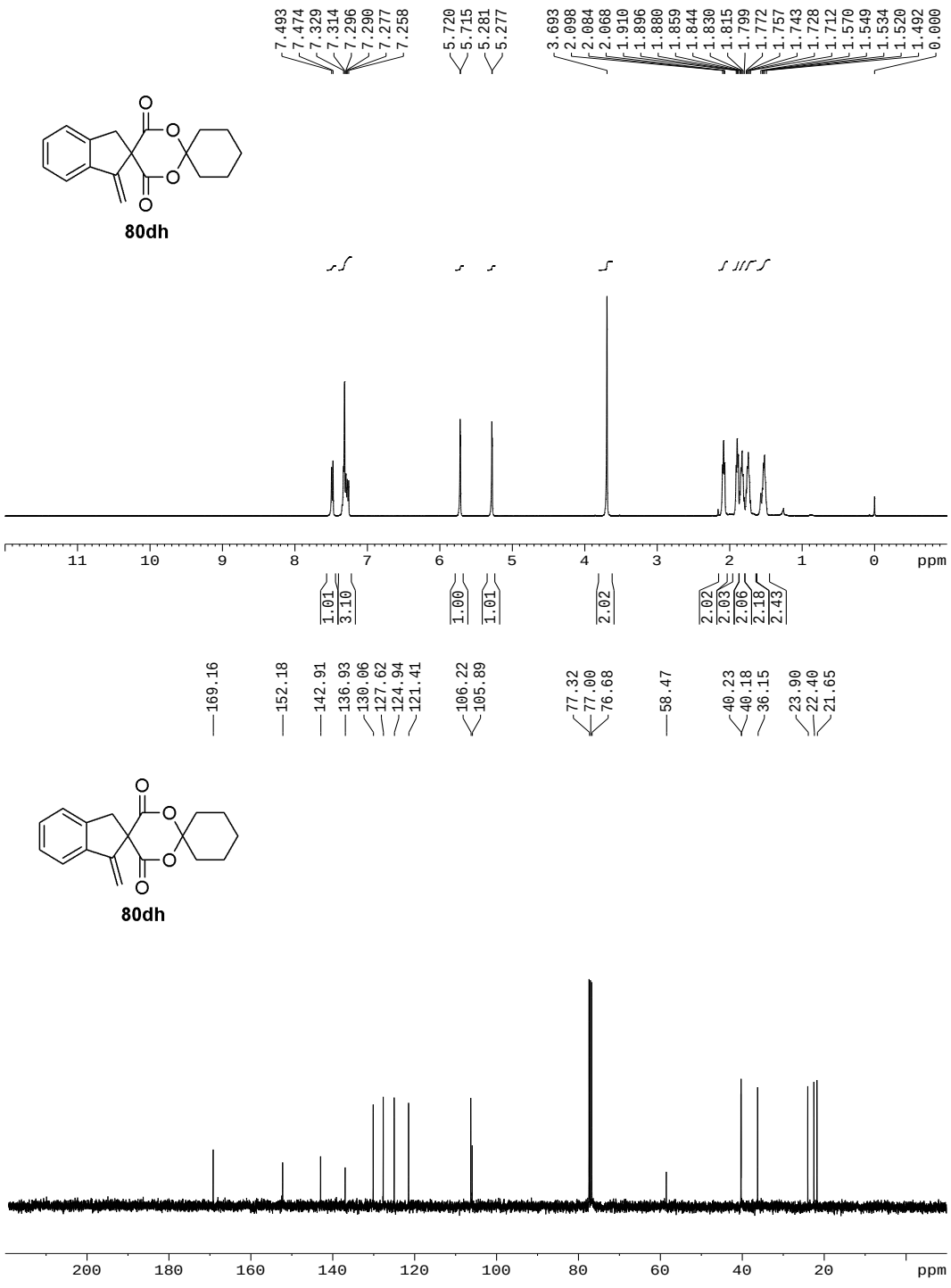


Figure-20: ^{1}H and ^{13}C NMR spectra of the product **80dh**

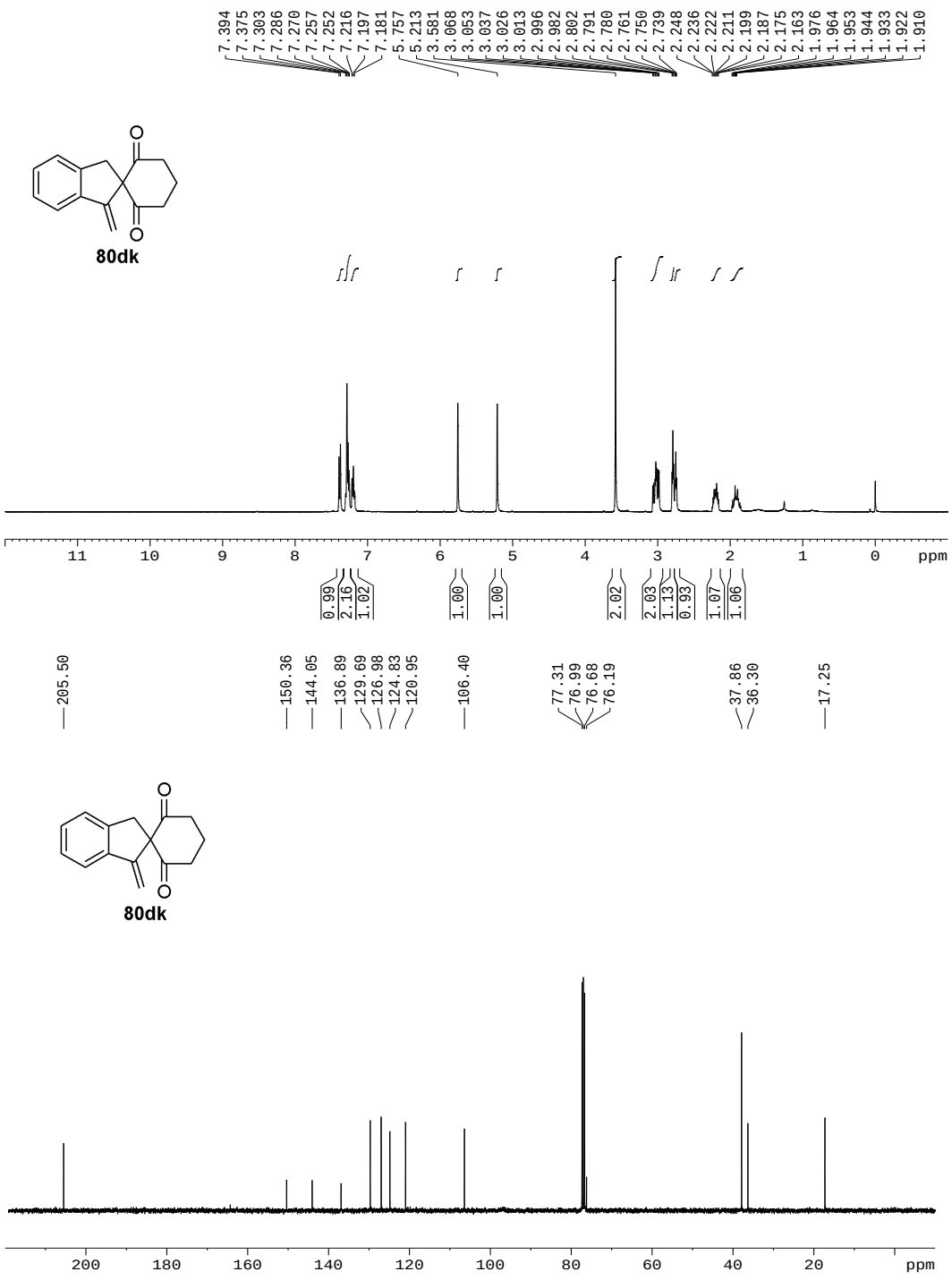


Figure-21: ^{1}H and ^{13}C NMR spectra of the product **80dk**

The three-component reaction was further extended into four-component heterocyclization reaction of **5d**, **20**, **77a** and ArN_3 **21a** and **21d** for the synthesis of 1,2,3-triazoles **81** by L-proline/$CuSO_4$/Na–(+)-ascorbate catalyses in one-pot as shown in Table 11. The reaction of **20d** with **5d** and **77a** under L-proline/self-catalyses in *t*-BuOH at 25 °C for 24 h furnished the cascade olefination/hydrogenation product **79dd** in 99% conversion, which upon *in situ* treatment with BnN_3 **21a** under $CuSO_4$/Na–(+)-ascorbate catalysis in *t*-BuOH and H_2O at 25 °C for 12 h selectively furnished 1,2,3-triazole **81dda** in 90% yield (Table 11). In a similar manner, treatment of *in situ* generated **79dj**, **79dk** and **79dm** with BnN_3 **21a** under $CuSO_4$/Na–(+)-ascorbate catalysis in *t*-BuOH and H_2O at 25 °C for 2–3 h in one-pot furnished 1,2,3-triazoles **81dja**, **81dka** and **81dma** in 75–78% yield, which are useful starting materials for pharmaceutical drug analogs **C** (see Figure-16).[58a] Interestingly, reaction of *in situ* generated **79db** with 1,4-bis(azidomethyl)benzene **21d** under $CuSO_4$/Na–(+)-ascorbate catalysis in *t*-BuOH and H_2O at 25 °C for 12 h in one-pot furnished 1,2,3-triazole **81dbd** in 73% yield, which could be a useful starting material for the generation of medium-sized rings. In all heterocyclization reactions, 10–15% of carbocyclization products **80** were furnished.

Next, this three-component carbocyclization reaction was applied in the synthesis of dialkyl 1-methyleneindan-2,2-dicarboxylates **80dga**–**dgb, 80dgf, 80dgi** in good yields (Table 12). Literature studies revealed that generation of acylcarbonylketenes **E** by cycloreversion of **D** can be achieved only at high temperatures[62] but alkyloxycarbonylketenes **E'** can be generated easily at ambient temperature by cycloreversion of **D'** and can be trapped by alcohols to furnish substituted malonates (Figure-23). This can be attributed to the electronic properties of **D'** which makes the rate of cycloreversion of **D'→E'** faster than that of **D→E**. Recently, we discovered this strategy for *in situ* generation and esterification of methoxycarbonyl ketenes with alcohols to furnish non-symmetrical malonates at ambient temperatures.[58e] Herein, the same strategy was employed for the sequential

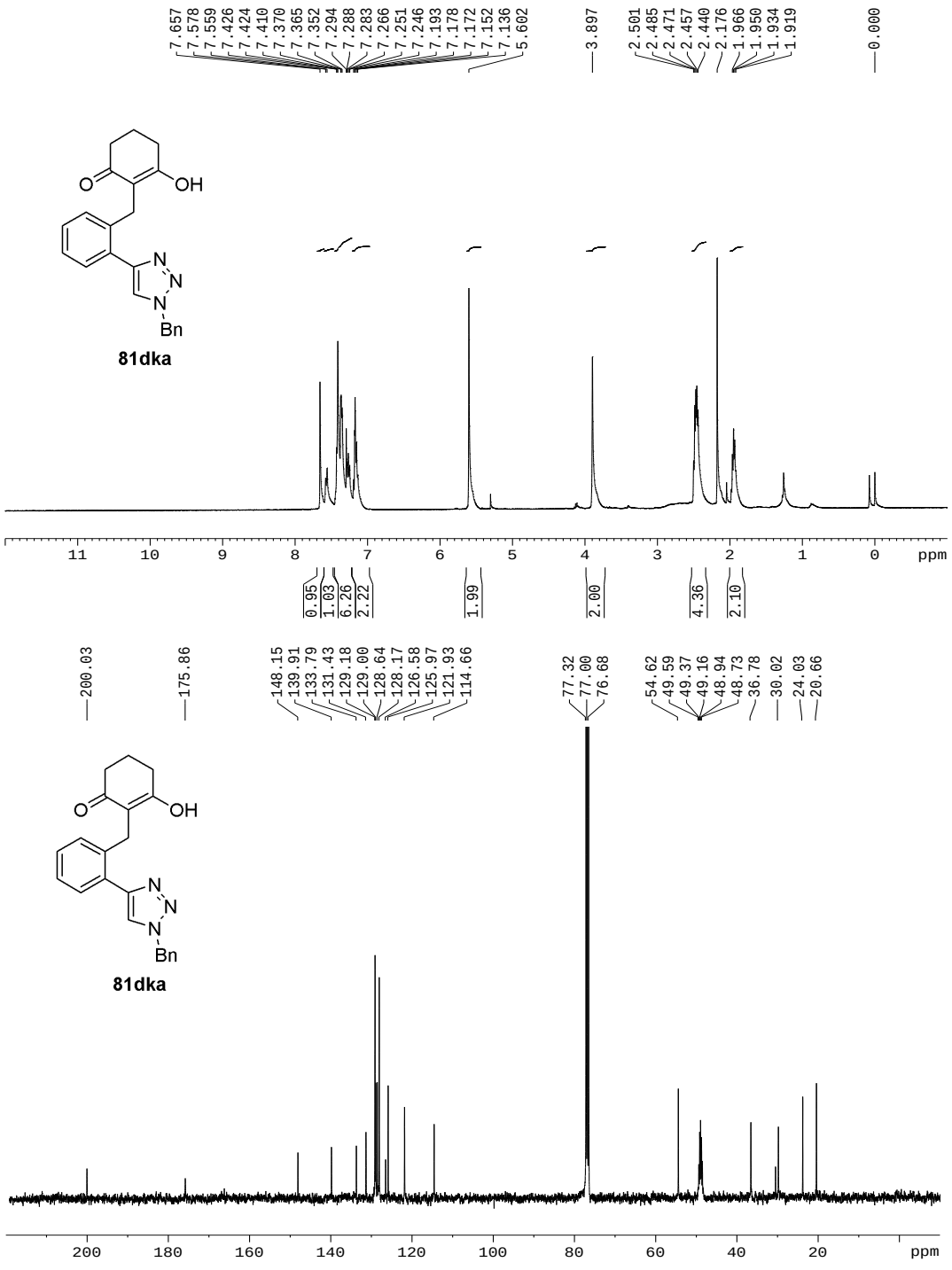


Figure-22: ^{1}H and ^{13}C NMR spectra of the product **81dka**

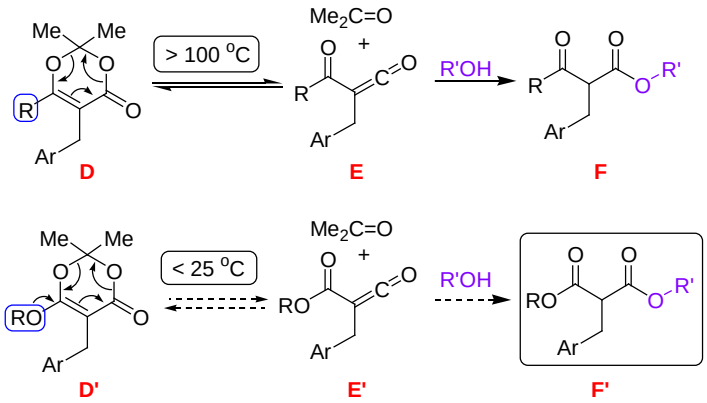


Figure-23: Synthesis of non-symmetrical malonates *via* alkyloxycarbonylketenes generated from 6-alkyloxy-[1,3]dioxin-4-one.

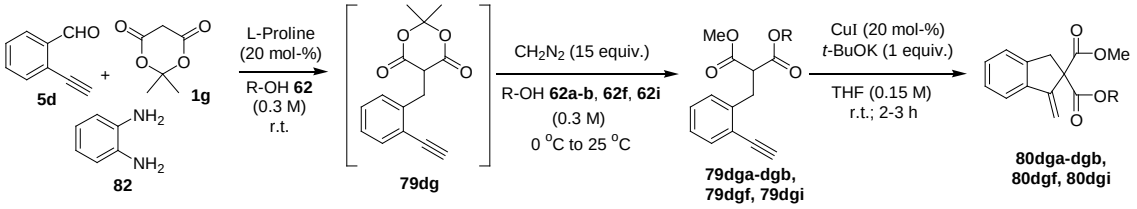
one-pot synthesis of malonates **79dga–dgb, 79dgf, 79dgi** from the olefination/ hydrogenation/alkylation/ketenization/esterification (O/H/A/K/E) reactions of **5d**, Meldrum's acid (**20g**), *o*-phenylenediamine (**82**), diazomethane and alcohols **62a–b, 62f, 62i** through iminium and self-catalysis in one-pot.[58e]

Interestingly, the L-proline/self-catalyzed cascade olefination/hydrogenation reaction of **20g** and **5d** (2 equiv.) with **82** in methanol (**62a**) at 25 °C for 0.5 h furnished **79dg** in 99% conversion which upon *in situ* treatment with ethereal diazomethane at 0 to 25 °C for 6 h furnished expected malonate **79dga** in 87% yield (Table 12, entry 1). In a similar manner, three more nonsymmetrical malonates **79dgb, 79dgf, 79dgi** were synthesized in good yield by performing the sequential O/H/A/K/E reactions in EtOH (**62b**), BnOH (**62f**) and *t*-BuOH (**62i**) solvents (Table 12, entries 2–4).

After successful preparation of malonates **79dga–dgb, 79dgf, 79dgi**, the carbocyclization reaction of **79dga** was screened under one of the optimized conditions (15 mol% of L-proline, 10 mol% of CuI, 2 equiv. of Cs_2CO_3, THF or CH_3CN, 25 °C, 12 h; Table A1). Surprisingly, no product formation was observed under these conditions and only starting material **79dga** was isolated. When the same carbocyclization reaction of **79dga** was performed using 30 mol% *t*-BuOK and 10

mol% of CuI in THF at 25 °C for 12 h, the rate of formation of **80dga** was very slow. When the catalyst loading was increased up to 20 mol% of CuI and 1 equiv. of *t*-BuOK in THF at 25 °C for 2 h, indene **80dga** was furnished in 80% yield (Table 12, entry 1). In a similar manner, three more nonsymmetrical indenes **80dgb, 80dgf, 80dgi** were synthesized in good yields by using the above conditions (Table 12, entries 2–4). Finally, sequential combination of cascade O/H/A/K/E and carbocyclization reactions were performed in one-pot to furnish indene **80dga** in 70% yield (Table 12, entry 5). Compound **80dgf** could be a suitable intermediate for the synthesis of pharmaceuticals **A** and **B** (see Figure-16), which emphasizes the value of this cascade approach.

Table 12: Synthesis of indene products through cascade O/H/A/K/E and carbocyclization reactions in one-pot



Entry	R-OH	Time/h		Product	Yield (%)[a]
		O/H step	A/K/E step		
1	MeOH **62a**	0.5	6	**79dga**	87
2	EtOH **62b**	0.5	2	**79dgb**	85
3	*t*-BuOH **62i**	0.5	2	**79dgi**	63
4	BnOH **62f**	0.5	6	**79dgf**	85
5[b]	MeOH **62a**	0.5	6	**79dga**	99%[c]

Entry	Time/h	Product	Yield (%)[a]
1	2	**80dga**	80
2	2	**80dgb**	75
3	2	**80dgi**	60
4	2	**80dgf**	70
5[b]	3	**80dga**	70

[a]Yield refers to the column-purified products and 2 equiv. of **5d** was used. [b]Reaction was performed in a sequential one-pot manner. [c]Conversion

With pharmaceutical applications in mind, drug intermediate **84dg** was synthesized from **83dg** through MCC reactions (Scheme 11). Recently, **84dg** was used as a key intermediate for the total synthesis of glucocorticoid receptor modulator **B** (Scheme 11).[56a] Herein, a combination of cascade olefination/hydrogenation/carbocyclization, base-induced decarboxylative isomerization, hydrogenation, alkylation and hydrolysis

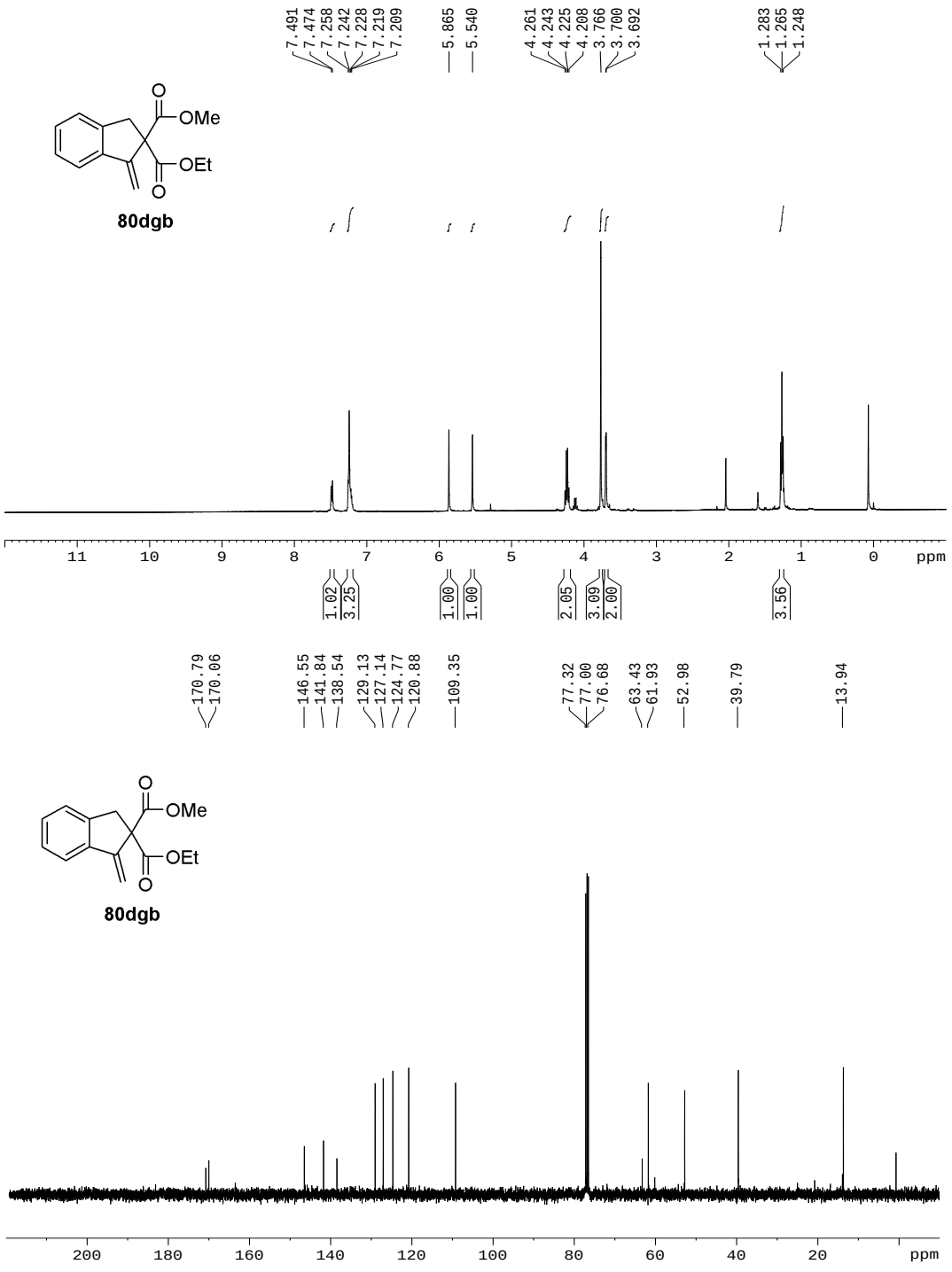
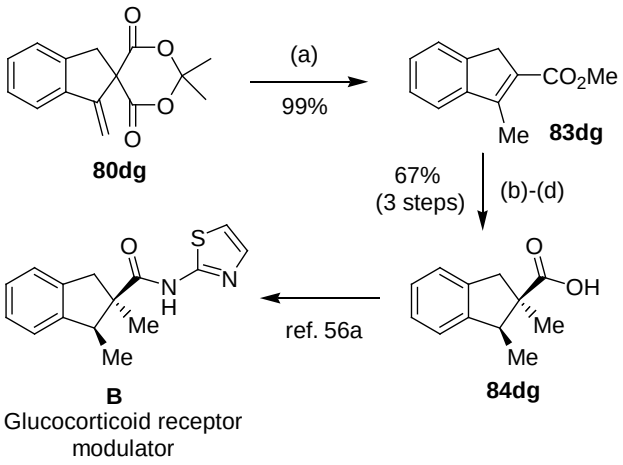


Figure-24: ^{1}H and ^{13}C NMR spectra of the product **80dgb**

reactions afforded **84dg** in only four synthetic steps with an overall yield of 66% and >90% *de* (Scheme 11). Synthesis of key intermediate **83dg** through the MCC reactions is evidently more advantageous over the existing methods where expensive heavy metal catalysts (Pd, Co, Re and Ru, etc.) or costly starting materials are used.[63]

Scheme 11: High yielding synthesis of glucocorticoid receptor modulator **B**



(a) KOH (1 equiv.), MeOH (0.05 M), 65–75 ^{o}C, 1 h, 99%; (b) 10% Pd/C (5 mol-%), EtOAc (0.1 M), 25 ^{o}C, 12 h, 99%; (c) DIPA (2.5 equiv.), n-BuLi (2.2 equiv.), MeI (4.5 equiv.), THF (0.25 M), –80 ^{o}C, 12 h, 88–90%; (d) 10% aq. KOH (1 equiv.), MeOH (0.25 M), 100 ^{o}C, 12 h, 75%.

The possible common mechanism for the synthesis of **80** and **81** from **79** with or without azides under L-proline/CuI/base catalyses is illustrated in Scheme 12. In the first step, catalyst L-proline selectively reacts with CuI to generate bidentate copper species [CuL], which is an active CuI species that reacts with acetylenes.[59a] In the following step, *in situ* generated [Cu^{A}L] selectively reacts with cascade olefination/hydrogenation product **79** to generate copper acetylide **85**. Mononuclear copper acetylide **85** further reacts with another active CuI species through π bonding to generate dinuclear alkynyl copper(I) complex **86** which is more reactive than **85** in heterocyclization reactions with azides, as revealed by kinetic data and DFT calculations obtained and performed by Fokin *et al.*[64]

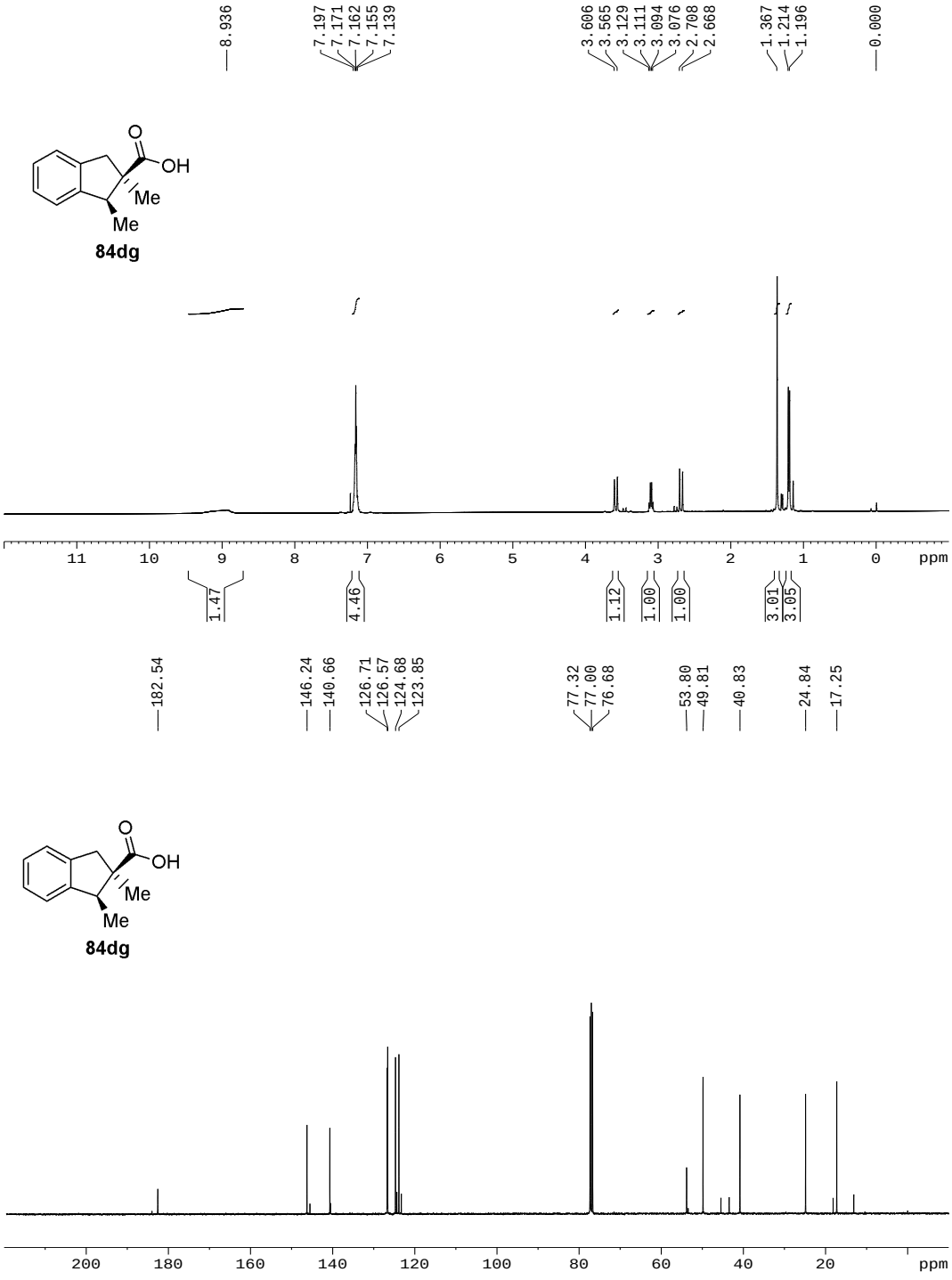
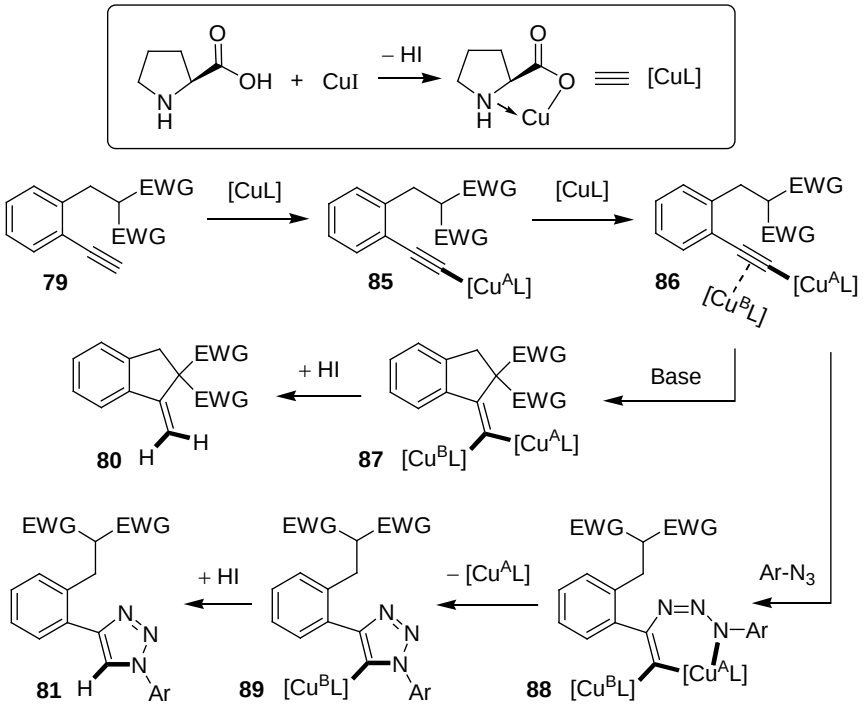


Figure-25: ^{1}H and ^{13}C NMR spectra of the product **84dg**

Scheme 12: Proposed reaction mechanism



Dinuclear alkynyl copper(I) complex **86** has dual activation modes, as it can react with two kinds of nucleophiles (soft and hard; Scheme 12). Base-induced *in situ* generated soft carbanion can undergo intramolecular cyclization to furnish dinuclear olefin **87** which upon oxidative addition with HI followed by reductive elimination can furnish expected carbocyclization product **80**. Intermolecular concerted [3+3] cycloaddition of active species **86** with hard alkyl azide heteronucleophiles can generate cupracycle **88** in the rate-determining step, which further undergoes reductive elimination to furnish mononuclear olefin **89**. Oxidative addition of **89** with HI followed by reductive elimination furnishes expected heterocyclization product **81**. The successful demonstration of two kinds of cyclizations on single substrate **79** under common copper catalysis, provided possible support to the existence of dinuclear alkynyl copper(I) complex **86** in click reactions.[64] π-Bonding of second copper complex [Cu^{B}L] with **85** is crucial and it acts as a Lewis acid for the intramolecular

carbocyclization reaction and also increases the rate of the reaction by stabilizing newly formed cupracycle **88** in heterocyclization reactions with organic azides (Scheme 12).

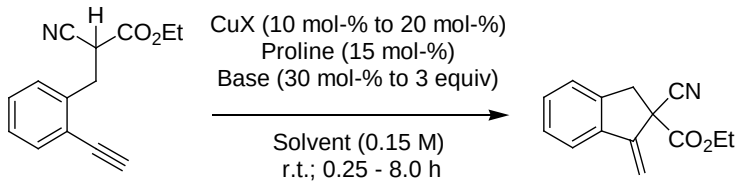
The existence of dinuclear alkynyl copper(I) complex **86** in MCC reactions was further supported by deuterium ion exchange experiment. When the cyclization reaction of **79db** and **79db** with BnN_3 **21a** was conducted under the catalysis of [CuL] in CH_3CN+D_2O or *t*-$BuOH+D_2O$ respectively at ambient conditions (Table A1, entries 15-17), the product **80db** was isolated with 40% deuterium exchange on olefin carbon (**80db**-D_2) and also product **81dba** was isolated with 60% deuterium exchange on the olefin carbon (**81dba**-D) as revealed by ^{1}H NMR and HRMS analysis. Importance of the reactivity of *in situ* generated dinuclear alkynyl copper(I) complex **86** was revealed by performing the CC reactions on compounds containing non-terminal alkynes **79ab**, **79aa** and **79aga** (Schemes A3-A8). Copper-catalyzed Conia-ene reactions performed on non-terminal alkynes (**79ab**, **79aa** and **79aga**) under different optimized conditions are not clean which may be due to the lack of dinuclear alkynyl copper(I) complex **86** formation.

6.3 CONCLUSION

In this chapter, a one-pot synthesis of indenes and 1,2,3-triazoles from common substrates and catalysts has been demonstrated through the "combination of multicomponent reactions (MCR) and multicatalytic cascade (MCC) reactions". With many points of diversity present in the products, this MCC process would be a powerful method for both indene/1,2,3-triazoles library generation and indene based target synthesis. Furthermore demonstration of the two kinds of cyclizations on a single substrate provides a possible support to the existence of dinuclear alkynyl copper(I) complex **86** in click reactions.

ANNEXURE-I: OPTIMIZATION OF CARBOCYCLIZATION REACTION

Table A1: Reaction optimization for the carbocyclization reaction of **79db**

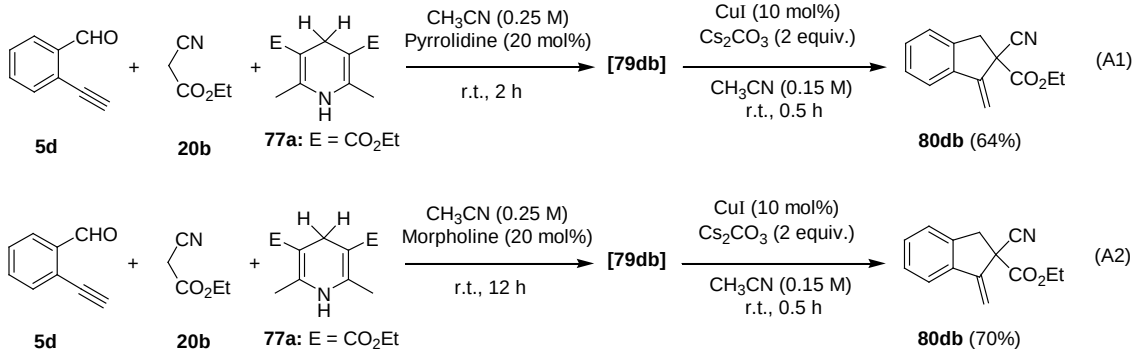


79db **80db**

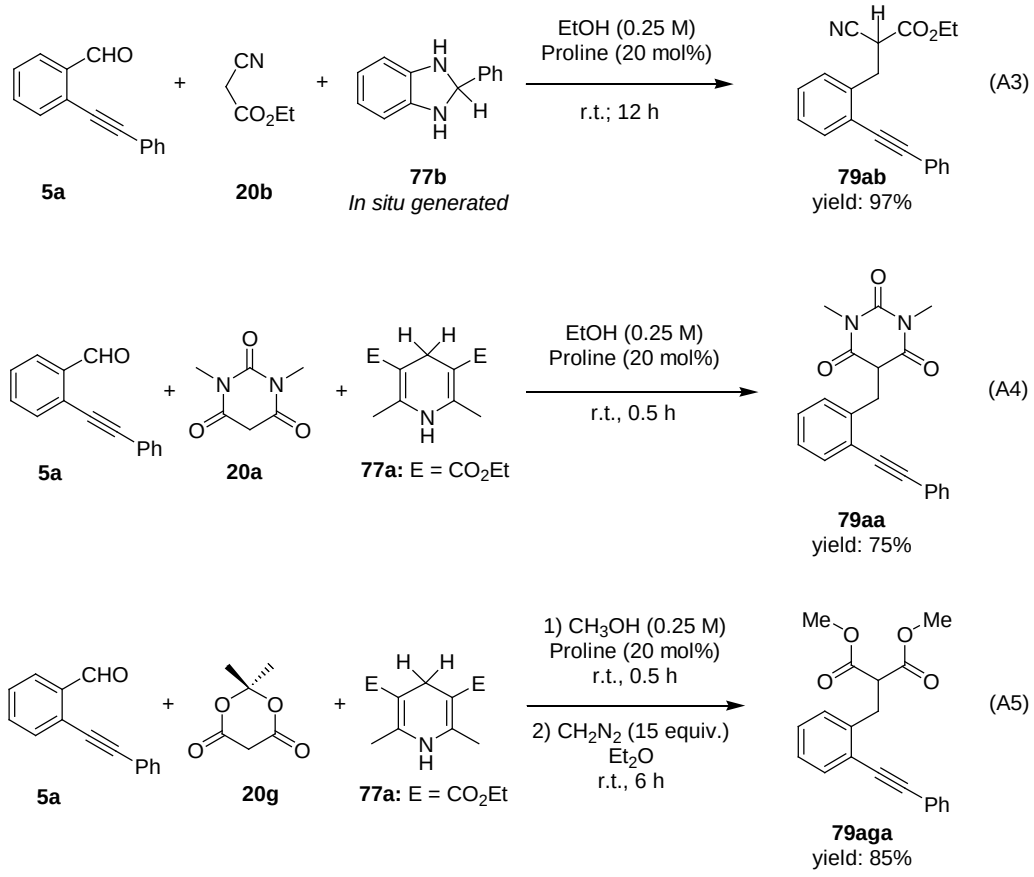
Entry	CuX (10 mol%)	Amino acid (15 mol%)	Base (equiv.)	Solvent (0.15 M)	Time (h)	Yield (%)[a] **80db**
1	–	–	Cs_2CO_3 (2)	THF	4	25
2	–	–	Cs_2CO_3 (2)	DMSO	1	40
3	CuI	–	Cs_2CO_3 (2)	DMSO	2	45
4[b]	CuI	–	*t*-BuOK (0.3)	THF	0.5	75
5[b]	CuI	–	*t*-BuOK (0.3)	DMSO	1	75
6	CuI	Proline	Cs_2CO_3 (3)	DMSO	0.25	75
7	CuI	Proline	Cs_2CO_3 (2)	DMSO	2	55
8	CuI	Proline	–	DMSO	8	–
9	**CuI**	**Proline**	**Cs_2CO_3 (2)**	**THF**	**0.5**	**90**
10	**CuI**	**Proline**	**Cs_2CO_3 (2)**	**CH_3CN**	**0.5**	**90**
11	CuI	Proline	Cs_2CO_3 (1)	THF	1	81
12	CuI	Proline	K_2CO_3 (2)	THF	1	80
13	CuCl	Proline	Cs_2CO_3 (2)	THF	0.5	80
14	CuBr	Proline	Cs_2CO_3 (2)	THF	0.5	90
15	**CuI**	**Proline**	**DIPEA (0.3)**	**CH_3CN**	**14**	**86**
16	**CuI**	**Proline**	**DIPEA (0.3)**	**$CH_3CN + H_2O$**	**20**	**70**
17	**$CuSO_4$**	**–**	**Na-Ascorbate (0.2)**	***t*-BuOH + H_2O**	**20**	**–**

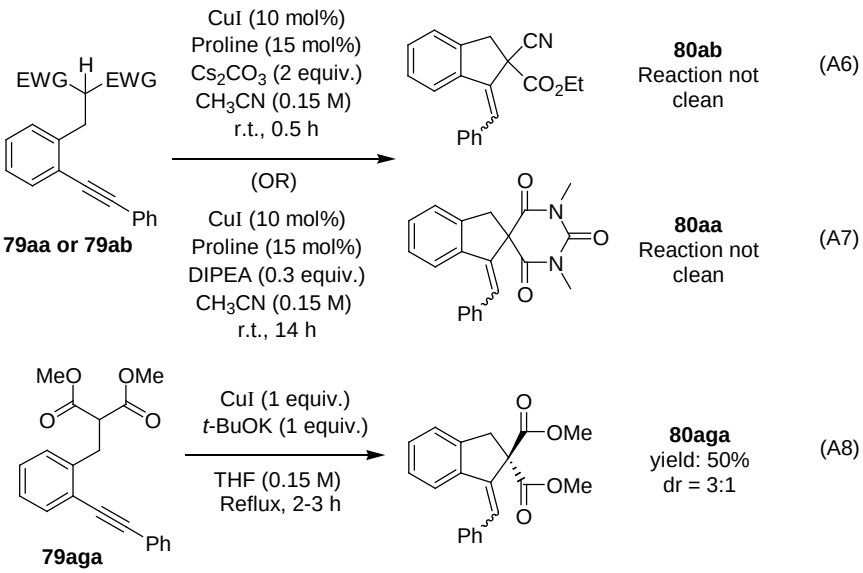
[a]Yield refers to the column-purified product. [b]20 mol-% of CuI was used.

Schemes A1-A2:



Schemes A3-A8: Multicomponent reactions (MCR) and multicatalytic cascade (MCC) reactions of non-terminal alkynylbenzaldehyde **5a**





80ab
Reaction not clean

(A6)

80aa
Reaction not clean

(A7)

80aga
yield: 50%
dr = 3:1

(A8)

7. RAPID TWO-STEP SYNTHESIS OF DRUG-LIKE POLYCYCLIC SUBSTANCES BY SEQUENTIAL MULTI-CATALYSIS CASCADE REACTIONS

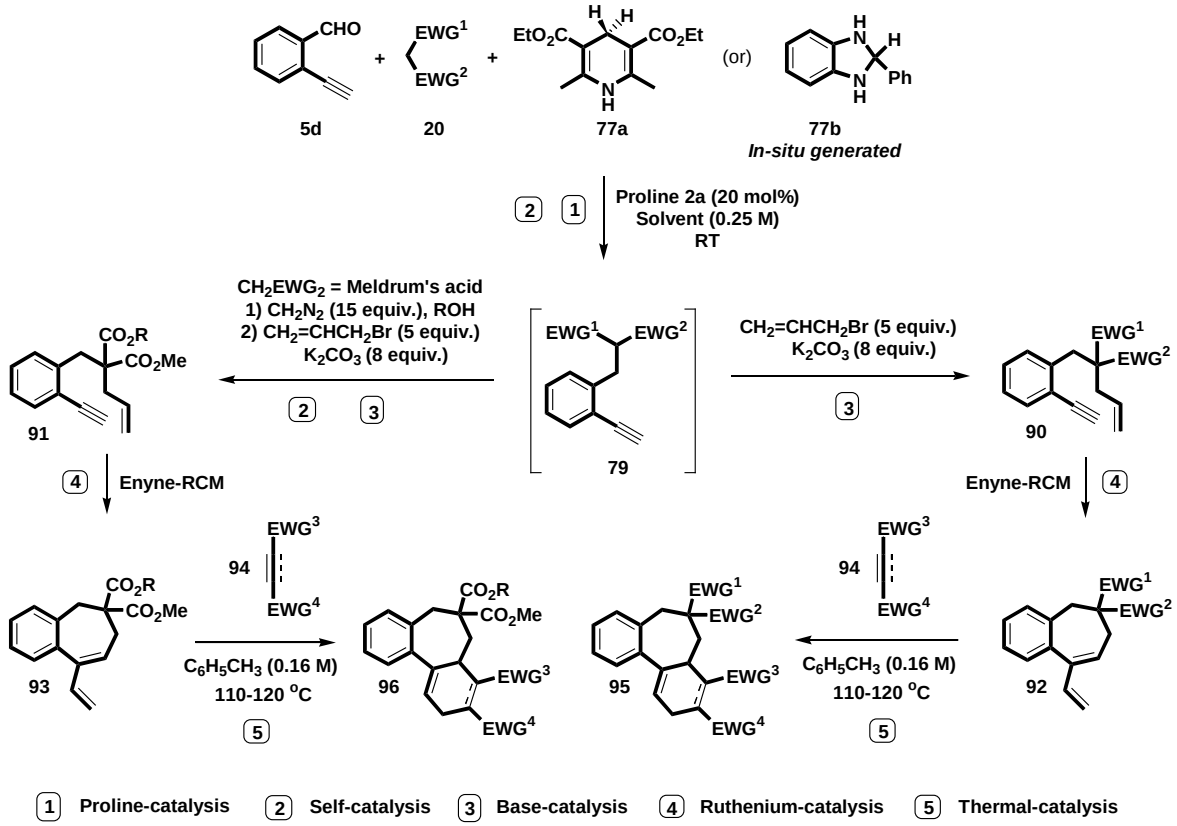
7.1 INTRODUCTION

Highly functionalized drug-like carbocycles are of considerable importance in the pharmaceutical industry.[65] As such, the development of new and more general green one-pot cascade methods for their preparation is of significant interest for the development of new drugs.[66a-i] Especially, functionalized polycyclic carbocycles have attracted considerable attention as a result of their structural complexity, biological activity and their presence in a variety of natural and unnatural products.[66j-l] Thus, the diversity-oriented synthesis of polycyclic carbocycles represents an important task because of the synthetic challenge and also because of widespread occurrence of such structural motifs and their use as building blocks.

Recently olefin metathesis of dienes and enynes catalyzed by Grubbs' catalysts provided a general platform to a variety of carbocycles with good yields.[67] The manifestation of olefin metathesis technology triggered a burst of activity in the synthesis of a huge variety of differently substituted carbocycles. On the other hand, the catalytic ability and orthogonal catalysis of L-proline to function as soft catalyst for cascade three-component reductive alkylation (TCRA) reactions has led to several examples, where combination of this TCRA reactions with other transformations in one-pot provided efficient new entries into useful drug intermediates.[68] In continuation of the above studies, it was envisaged that TCRA strategy could be combined with olefin metathesis strategy to provide highly functionalized polycyclic compounds in a cascade approach.

Hence, a novel and green technology was discovered for the two-step synthesis of highly substituted drug-like carbocycles **95** and **96** using proline-/self-/potassium carbonate-/ruthenium-/thermal-catalysis through cascade TCRA, *C*-A, enyne-RCM and DA reactions as key steps starting from commercially available 2-ethynyl-benzaldehydes **5**, CH-acids **20**, organic-hydrides **77**, allyl bromide, diazomethane, reactive dienophiles **94**, L-proline **2a**, K_2CO_3 and Grubbs' 1st or 2nd generation ruthenium catalysts, an approach called "multi-catalysis cascade (MCC) approach to carbocycles" (Scheme 13).[58,68] Herein, this new synthetic strategy of combining organocatalysis with enyne-RCM/DA reactions to deliver complex carbocycles from a two-step cascade sequence is presented (Scheme 13).

Scheme 13: Synthesis of drug like carbocycles via a two-step sequence



7.2 RESULTS AND DISCUSSION

Amino acid L-proline **2a** was found to readily catalyze the olefination of **5d** with ethyl cyanoacetate **20b** to furnish the active olefin, which on *in situ* treatment with Hantzsch ester **77a** produced the TCRA product **79db** with very good conversion in EtOH or DMSO at 25 °C for 1 h. Further treatment of **79db** with allyl bromide and K_2CO_3 at 25 °C for 11 h furnished the ene-yne product **90db** with 95% yield. The same sequential cascade TCRA/*C*-A reaction with *in situ* generated hydride source, 2-phenyl-2,3-dihydro-1*H*-benzoimidazole **77b** also furnished the product **90db** with 93% yield (Table 13, entry 1). The optimum conditions involved the usage of 20 mol% catalyst **2a** and 8 equiv. of K_2CO_3 in cascade TCRA/*C*-A reaction of **5d**, **20b**, **77a**/**77b** and allyl bromide in EtOH or DMSO at 25 °C to furnish **90db** in very good yield.

The scope of this sequential one-pot cascade TCRA/*C*-A reactions was investigated by treating a variety of CH-acids **20a–g, 20j-l, 20n-o** with 1 equiv. of 2-ethynyl-benzaldehyde **5d**, 1 equiv. of organic hydride **77a**/**77b** and 5 equiv. of allyl bromide under the sequential catalysis by 20 mol% of L-proline/self and K_2CO_3 in DMSO at 25 °C for 0.75 to 24 h (Table 13). Acyclic and cyclic CH-acids **20a–g, 20j-l, 20n-o** afforded the expected ene-yne products **90** with excellent yields (Table 13). Reaction of (1*R*,2*S*,5*R*)-cyano-acetic acid 2-isopropyl-5-methyl-cyclohexyl ester **20e** with **5d**, **77b** and allyl bromide under L-proline/self/K_2CO_3-catalysis furnished the product (-)-**90de**, but unfortunately with only 1 : 1 dr (Table 13, entry 6).

Reaction of Meldrum's acid **20g** with **5d**, **77a** and allyl bromide under L-proline/self/K_2CO_3-catalyses furnished the product **90dg** in 76% yield (Table 13, entry 8). In a similar manner, ene-yne compound **90da** was furnished as the major product with 60% yield (Table 13, entry 12). Interestingly, reaction of cyclic CH-acids **20j–l** with **5d**, **77a** and allyl bromide under L-proline/self/ K_2CO_3 catalyses furnished the ene-

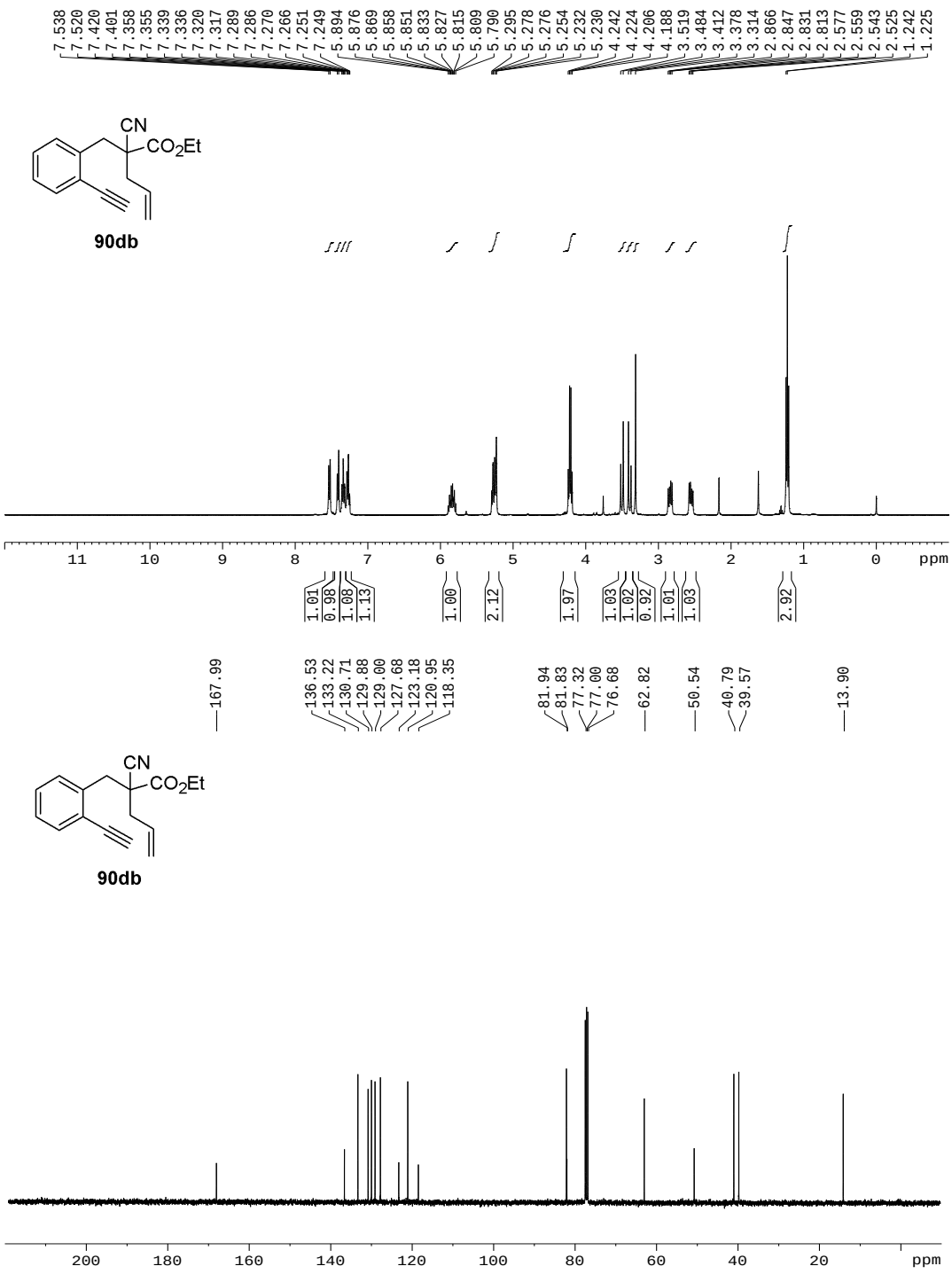
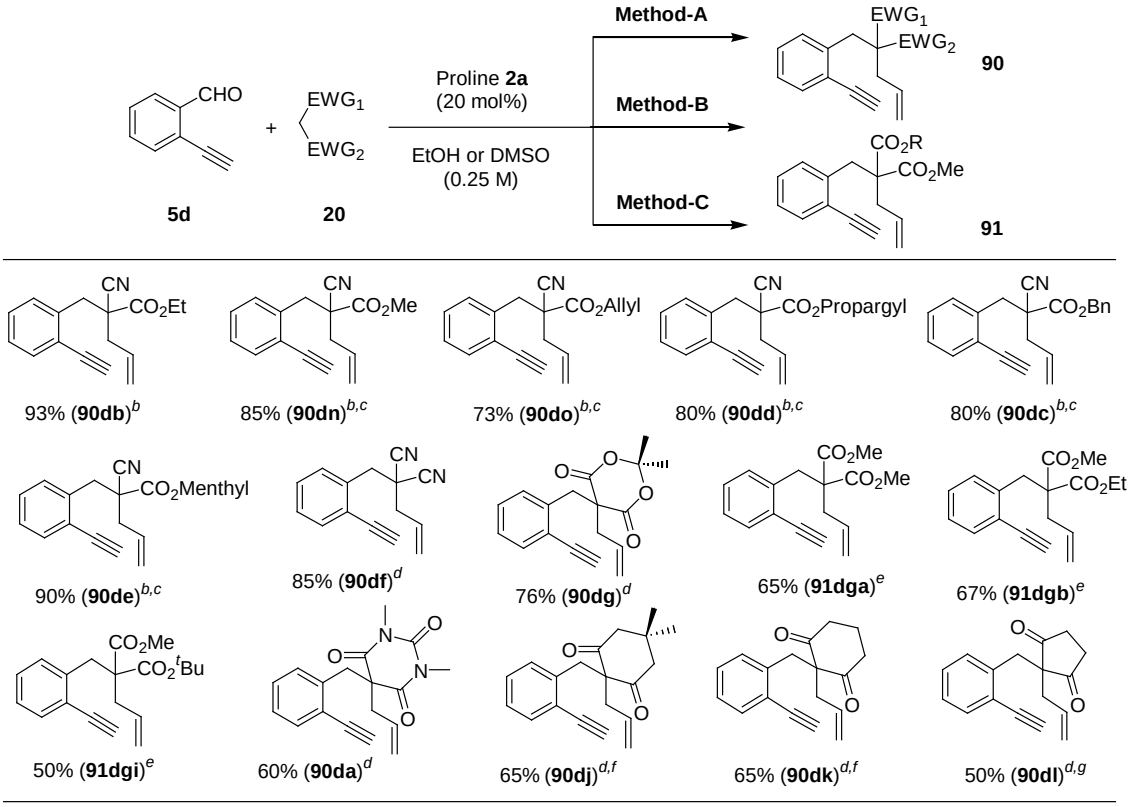


Figure-26: ^{1}H and ^{13}C NMR spectra of the product **90db**

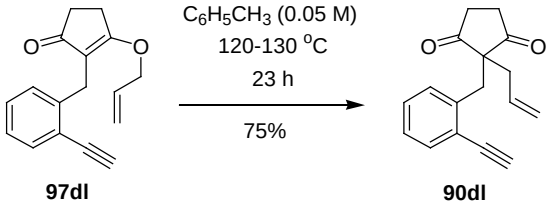
Table 13: Sequential multi-catalytic cascade approach to ene-ynes **90/91**[a]



[a]Yield refers to the column-purified products. [b]Method-A: A mixture of **5d** (0.3 mmol), **20** (0.3 mmol) and proline **2a** (20 mol%) in EtOH (0.25 M) was stirred at room temperature for 0.5-11 h. Then *o*-phenylenediamine (0.3 mmol) and PhCHO (0.3 mmol) were added and stirring was continued at the same temperature for 1.5-16 h. Then solvent was evaporated and CH_2=$CHCH_2Br$ (5 equiv.), K_2CO_3 (8 equiv.) and DMSO (0.25 M) were added and stirring was continued at the same temperature for 0.25-11 h. [c]DMSO was used as solvent throughout the reaction sequence. [d]Method-B: A mixture of **5d** (0.3 mmol), **20** (0.3 mmol), **77a** (0.3 mmol) and proline **2a** (20 mol%) in EtOH (0.25 M) was stirred at room temperature for 0.75-24 h. Then solvent was evaporated and CH_2=$CHCH_2Br$ (5 equiv.), K_2CO_3 (8 equiv.) and DMSO (0.25 M) were added and stirring was continued at the same temperature for 0.5-1 h. [e]Method-C: All reactants **5d**, **20g**, **77a** and catalyst **2a** were mixed at the same time in R-OH **62a-b, 62i** and stirred at 25 °C, then 15 equiv. of ethereal diazomethane was added and stirred at 25 °C for 2-6 h. Then solvent was evaporated and CH_2=$CHCH_2Br$ (5 equiv.), K_2CO_3 (6 equiv.) and DMSO (0.25 M) were added and stirring was continued at the same temperature for 12 h. [f]25-30% of *O*-allylated (*O*-A) products **97dj** or **97dk** were formed. [g]50% of *O*-allylated (*O*-A) product **97dl** was formed.

yne compounds **90dj–dl** as major products in 50–65% yields accompanied by TCRA/*O*-A by-products **97dj–dl** in 25–50% yields as shown in Table 13, entries 13–15. This may be due to the highly acidic nature of cyclic CH-acids **20j–l** compared to acyclic CH-acids **20b–f, 20n–o** in the compounds **79dj–dl**. By-products **97dj–dl** can be

converted into required ene-yne compounds **90dj–dl** by thermal-catalysis through Claisen rearrangement. As expected, by-product **97dl** was transformed into ene-yne **90dl** in 75% yield after heating at 120 °C for 23 h in toluene as shown in Eq. 2. Structure of products **90da–dg, 90dj–dl, 90dn–do** were confirmed by NMR and mass analyses.



97dl **90dl** (Eq. 2)

For the synthesis of ene-ynes **91dga–dgb, 91dgi** containing malonates, the strategy of *in situ* generation and esterfication of methoxycarbonylketenes with alcohols, was utilized. The sequential cascade TCRA-/alkylation-/ketenization-/esterification (TCRA/A/K/E) followed by *C*-allylation (*C*-A) reactions of 2-ethynyl-benzaldehyde **5d**, Meldrum's acid **20g**, Hantzsch ester **77a**, diazomethane, alcohols **62a**–**b, 62i** and allyl bromide afforded the ene-ynes containing malonates *via* iminium-/self-/self-/self-/self-/base-catalysis in one-pot.[58e] Interestingly, L-proline-/self-catalyzed cascade TCRA reaction of Meldrum's acid **20g** and 2-ethynyl-benzaldehyde **5d** with organic-hydride **77a** in MeOH **62a** at 25 °C for 1 h furnished the expected TCRA product **79dg** in >99% conversion, which on *in situ* treatment with ethereal diazomethane at 0 °C → 25 °C for 2 h furnished the expected dimethyl-2-(2-ethynyl-benzyl)-malonate **79'dga** with 99% conversion, which on *in situ* treatment with allyl bromide and K_2CO_3 furnished the expected ene-yne compound **91dga** in 65% yield (Table 13, entry 9). In a similar manner, two more ene-ynes **91dgb, 91dgi** were synthesized with good yields by performing the sequential TCRA/A/K/E/*C*-A reactions in EtOH **62b** and *t*-BuOH **62i** solvents respectively as shown in Table 13, entries 10 and 11.

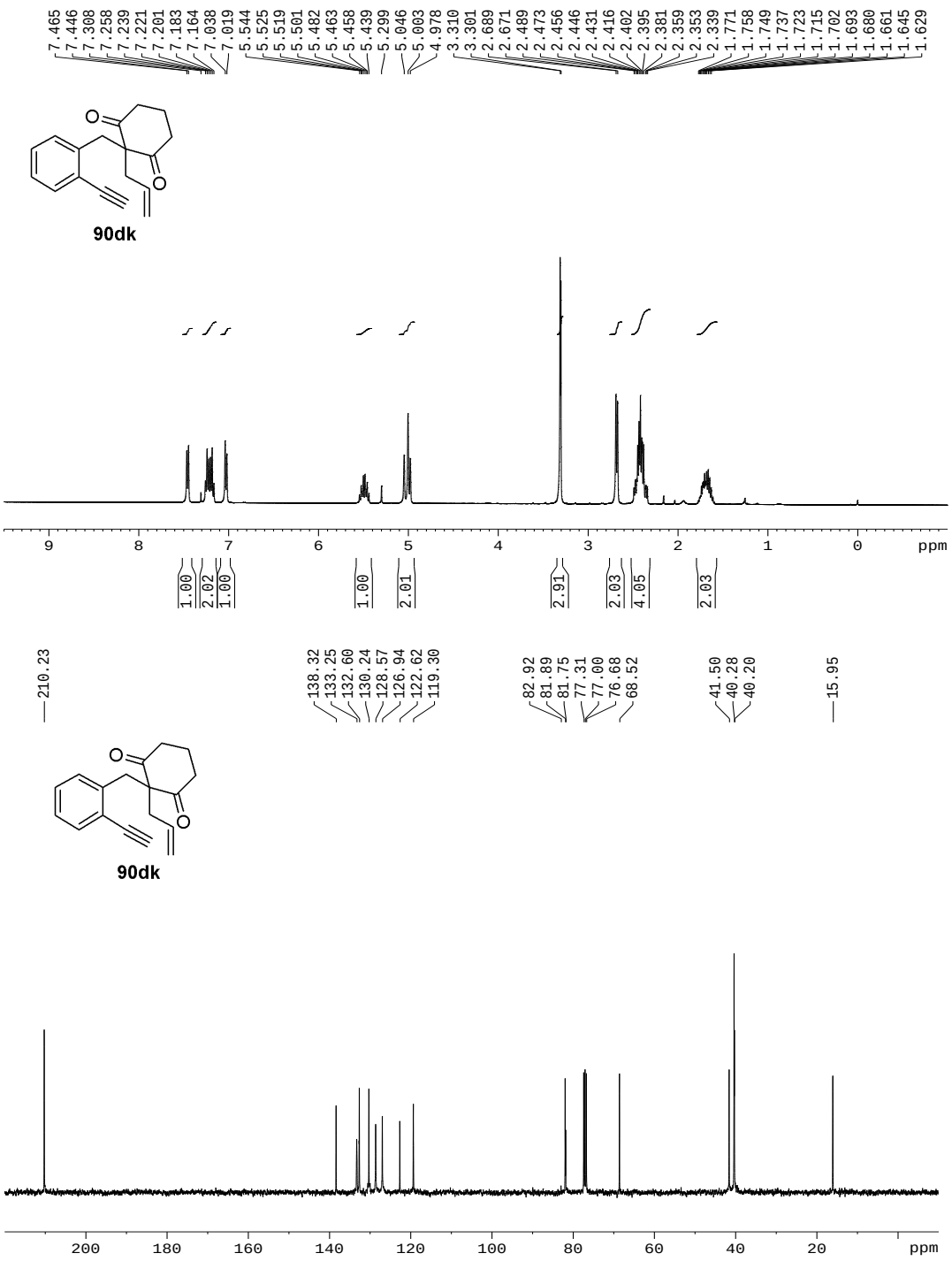


Figure-27: ^{1}H and ^{13}C NMR spectra of the product **90dk**

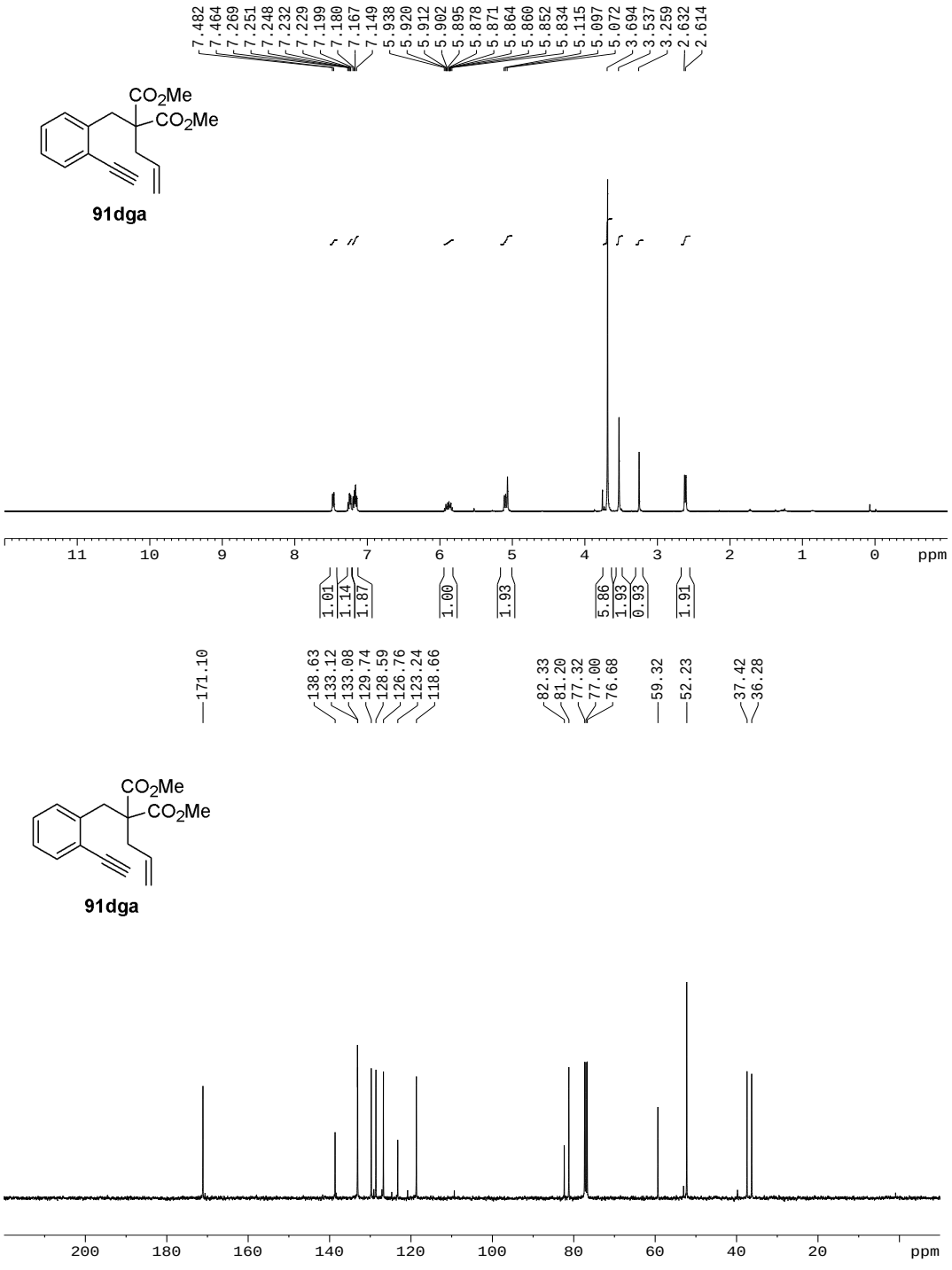
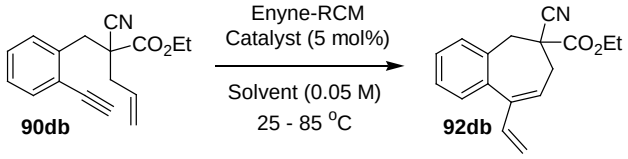


Figure-28: ^{1}H and ^{13}C NMR spectra of the product **91dga**

After synthesizing a diversity oriented library of the ene-yne compounds, the optimization of enyne-RCM reaction on **90db** was carried out by changing reactions conditions as shown in Table 14. Interestingly, the enyne-RCM reaction of **90db** using Grubbs' 1st generation catalyst in CH_2Cl_2 at 25 °C for 14 h furnished the highly functionalized benzocycloheptene **92db** in 55% yield and the same reaction using Grubbs' 2nd generation catalyst also furnished **92db** in 55% yield (Table 14, entries 1 and 2). Enyne-RCM reaction of **90db** with Hoveyda-Grubbs' 1st generation catalyst in CH_2Cl_2 at 25 °C for 11 h was not superior as compared to Grubbs' 1st generation catalyst (Table 14, entry 3). Surprisingly, the expected product was not formed when the enyne-RCM reaction of **90db** was performed employing $PtCl_2$ as catalyst in $C_6H_5CH_3$ at 25/85 °C for 21 h as shown in Table 14, entries 7 and 8.[66f]

Table 14: Optimization of enyne-RCM reaction



90db **92db**

entry	catalyst (5 mol%)	solvent (0.05 M)	temp (°C)	time (h)	yield (%)[a]
1	Grubbs' 1st generation	CH_2Cl_2	25	14	55
2	Grubbs' 2nd generation	CH_2Cl_2	25	11	55
3[b]	Hoveyda-Grubbs' 1st generation	CH_2Cl_2	25	11	34
4	Grubbs' 1st generation	CH_2Cl_2	45	5	63
5[b]	Grubbs' 1st generation	$PhCH_3$	85	2	45
6	Grubbs' 2nd generation	CH_2Cl_2	45	7	59
7[c]	$PtCl_2$	$PhCH_3$	25	21	–
8[d]	$PtCl_2$	$PhCH_3$	85	21	–

[a]Yield refers to the column-purified products. [b]Reaction conversion is only 50-60%.
[c]Ene-yne **90db** was recovered. [d]Starting material **90db** was decomposed.

Interestingly, enyne-RCM reaction of **90db** using Grubbs' 1st generation catalyst in CH_2Cl_2 at 45 °C for 5 h furnished the benzocycloheptene **92db** in 63% yield; but the

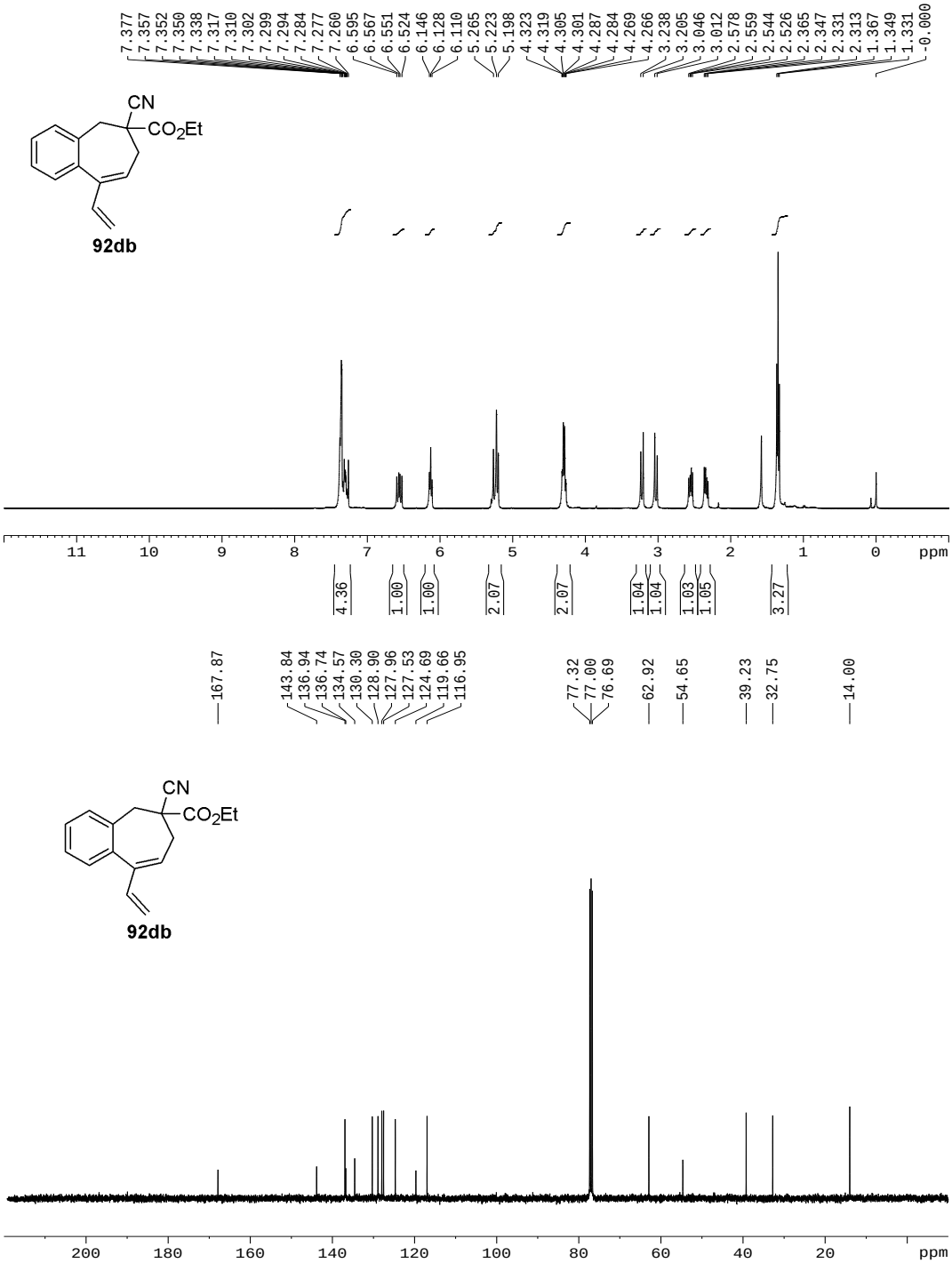
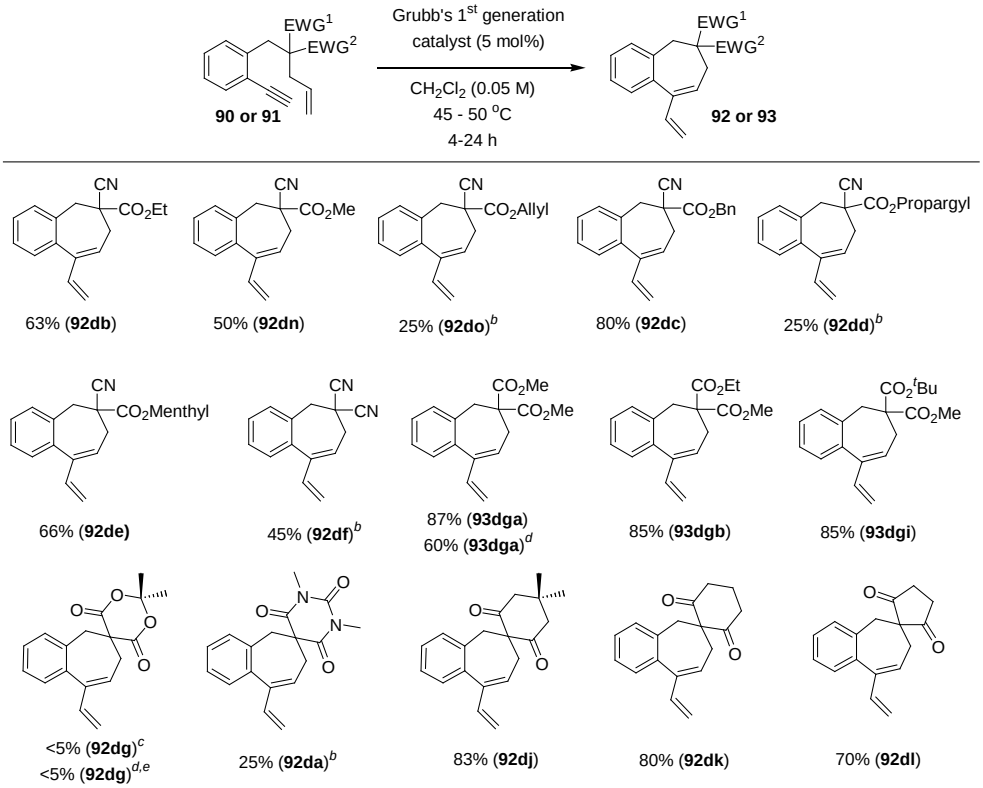


Figure-29: ^{1}H and ^{13}C NMR spectra of the product **92db**

same reaction under similar reaction conditions using Grubbs' 2nd generation catalyst furnished **92db** with only 59% yield (Table 14, entries 4 and 6). The optimum conditions involved the usage of 5 mol% Grubbs' 1st generation catalyst in enyne-RCM reaction of **90db** in CH_2Cl_2 at 45 °C for 5 h to furnish **92db** with good yield

With the optimized reaction conditions, the scope of the ruthenium-catalyzed enyne-RCM reactions was investigated with a variety of functionalized ene-ynes **90**/**91** as shown in Table 15. A series of ene-ynes **90** were converted into benzocycloheptenes **92da–dg, 92dj**–**dl, 92dn**–**do** in moderate to good yields (Table 15).

Table 15: Synthesis of enyne-RCM products **92/93**[a]



[a]Yield refers to the column-purified products. [b]Reaction conversion is only 50-60%. [c]Ene-yne **90dg** was recovered. [d]Reaction conditions: $PtCl_2$ (5 mol%), $C_6H_5CH_3$ (0.05 M), 110 °C, 5 h. [e]Starting material **90dg** was decomposed.

Interestingly, enyne-RCM reaction of diene-yne **90do** using Grubbs' 1st generation catalyst (5 mol%) in CH_2Cl_2 at 45 °C for 5 h furnished the product **92do** chemoselectively in 50–60% conversion and 25% yield (Table 15, entry 3). In a similar manner, chemoselective enyne-RCM reaction of ene-diyne **90dd** using Grubbs' 1st generation catalyst (5 mol%) in CH_2Cl_2 at 45 °C for 8 h furnished the product **92dd** in 50–60% conversion and 25% yield (Table 15, entry 5). Enyne-RCM reaction of a 1 : 1 dr mixture of chiral compound (-)-**90de** furnished the expected benzocycloheptene (-)-**92de** in 66% yield with 1 : 1 dr mixture as shown in Table 15, entry 6. Unfortunately, enyne-RCM reaction on Meldrum's acid containing ene-yne **90dg** didn't afford the expected product **92dg** even after screening two different reaction conditions as shown in Table 15, but the similar reaction on barbituric acid containing ene-yne **90da** furnished the expected spiro-benzocycloheptene **92da** in moderate yield as shown in Table 15. Enyne-RCM reaction of cyclic ene-ynes **90dj–dl** using Grubbs' 1st generation catalyst (5 mol%) in CH_2Cl_2 at 45 °C for 5 h furnished the spiro-products **92dj–dl** in 70–83% yields (Table 15, entries 13–15).

For the rapid high-yielding one-pot synthesis of complex drug like molecules and with synthetic/pharmaceutical applications in mind, the amino acid-/self-/K_2CO_3-/[Ru]-promoted cascade TCRA/*C*-A/enyne-RCM products **92da–dg, 92dj–dl, 92dn–do** were transformed into a novel class of highly substituted polycyclic substances **95** and **96** through a cascade TCRA/*C*-A/enyne-RCM/DA reaction sequence (Table 16). Simple acyclic substance, 2-ethynyl-benzaldehyde **5d** was converted into highly functionalized spiro-polycyclic *endo* product **95dja** with >99% de in stereoselective manner with 55.9% overall yield through a sequence of amino acid-/self-/K_2CO_3-catalyzed cascade TCRA/*C*-A, ruthenium-promoted enyne-RCM followed by heat-promoted Diels-Alder (DA) reaction with 1-phenyl-pyrrole-2,5-dione **94a** in one-pot as shown in Table 16, entry 1. Generality of the amino acid-/self-/K_2CO_3-/[Ru]-/heat-

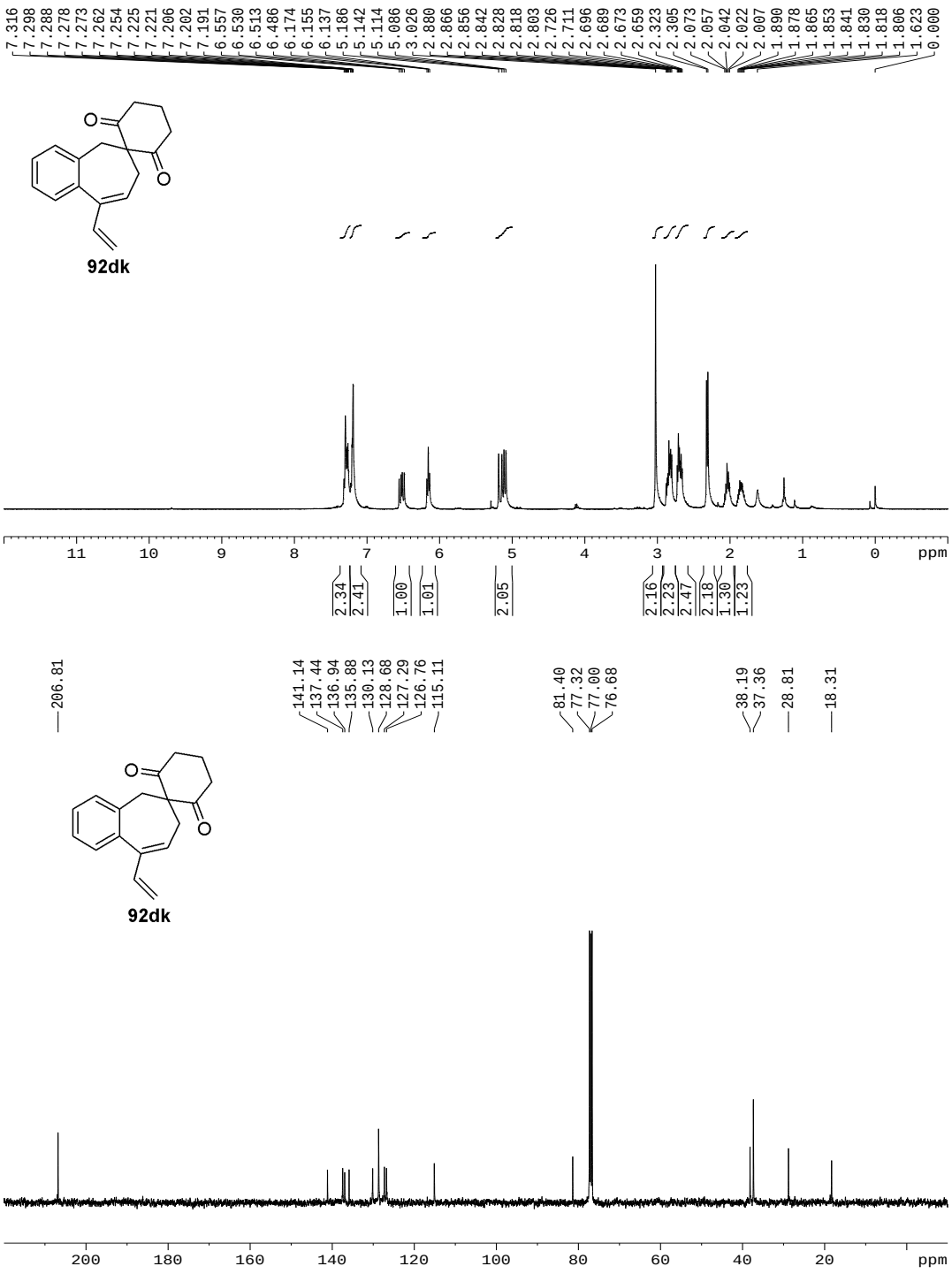


Figure-30: ^{1}H and ^{13}C NMR spectra of the product **92dk**

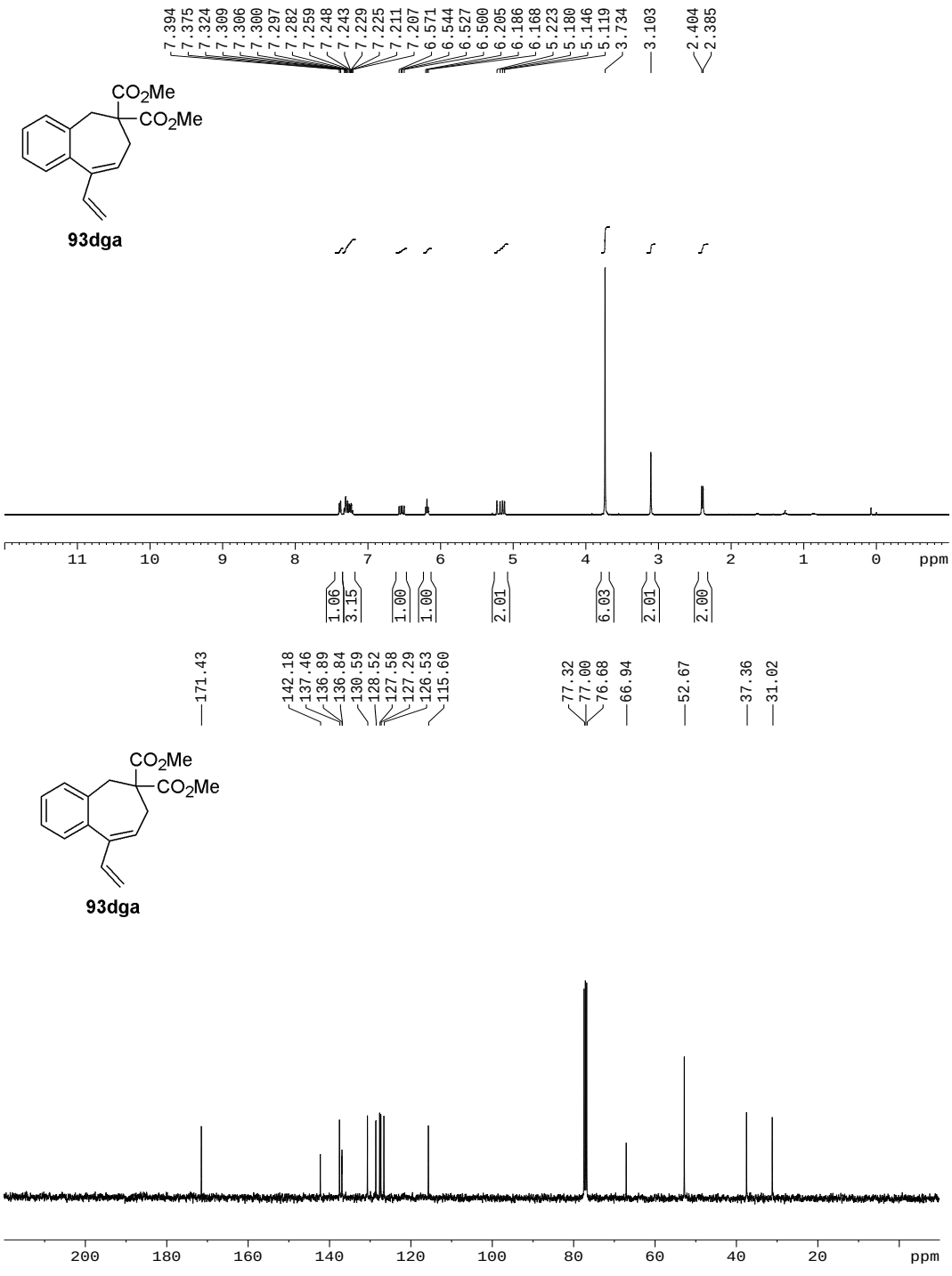
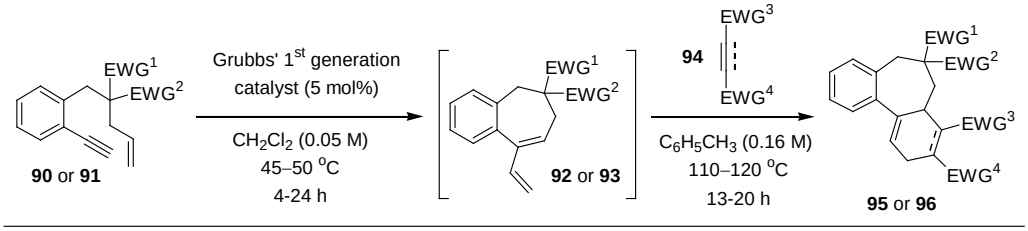
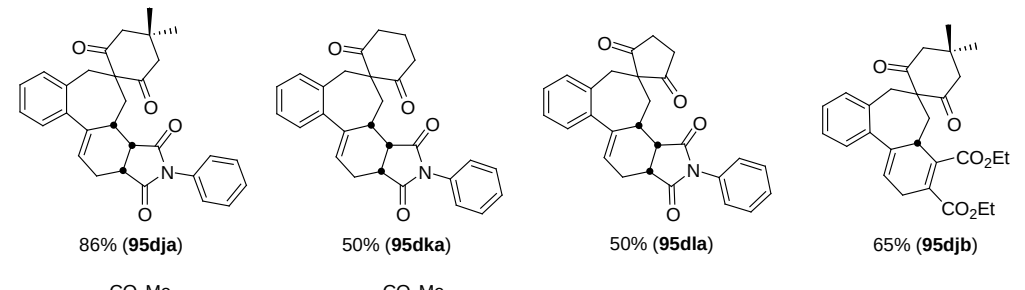


Figure-31: ^{1}H and ^{13}C NMR spectra of the product **93dga**

promoted stereoselective sequential one-pot cascade TCRA/*C*-A or TCRA/A/K/E/*C*-A, enyne-RCM and DA reactions was further confirmed by four more examples using different CH-acids **20** and dienophile **94a** to furnish the expected highly functionalized polycyclic *endo*-product **95dka** in 32.5% overall yield with >99% de, *endo*-product **95dla** in 25.0% overall yield with >99% de, *endo*-product **96dga$_2$** in 48.75% overall yield with >99% de, and *endo*-product **96dgba** in 57.0% overall yield with ≤5% de, respectively as shown in Table 16. Structure and stereochemistry of polycyclic substances **95**–**96** were confirmed by NMR analysis and also by mass analysis. This two-step sequential MCC reaction could be employed for generating a diversity-oriented library of polycyclic substances **95**/**96** which are useful for pharmaceutical applications.

Table 16: One-pot assembly of drug-like polycyclic substances **95/96** from simple acyclic molecules[a]





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

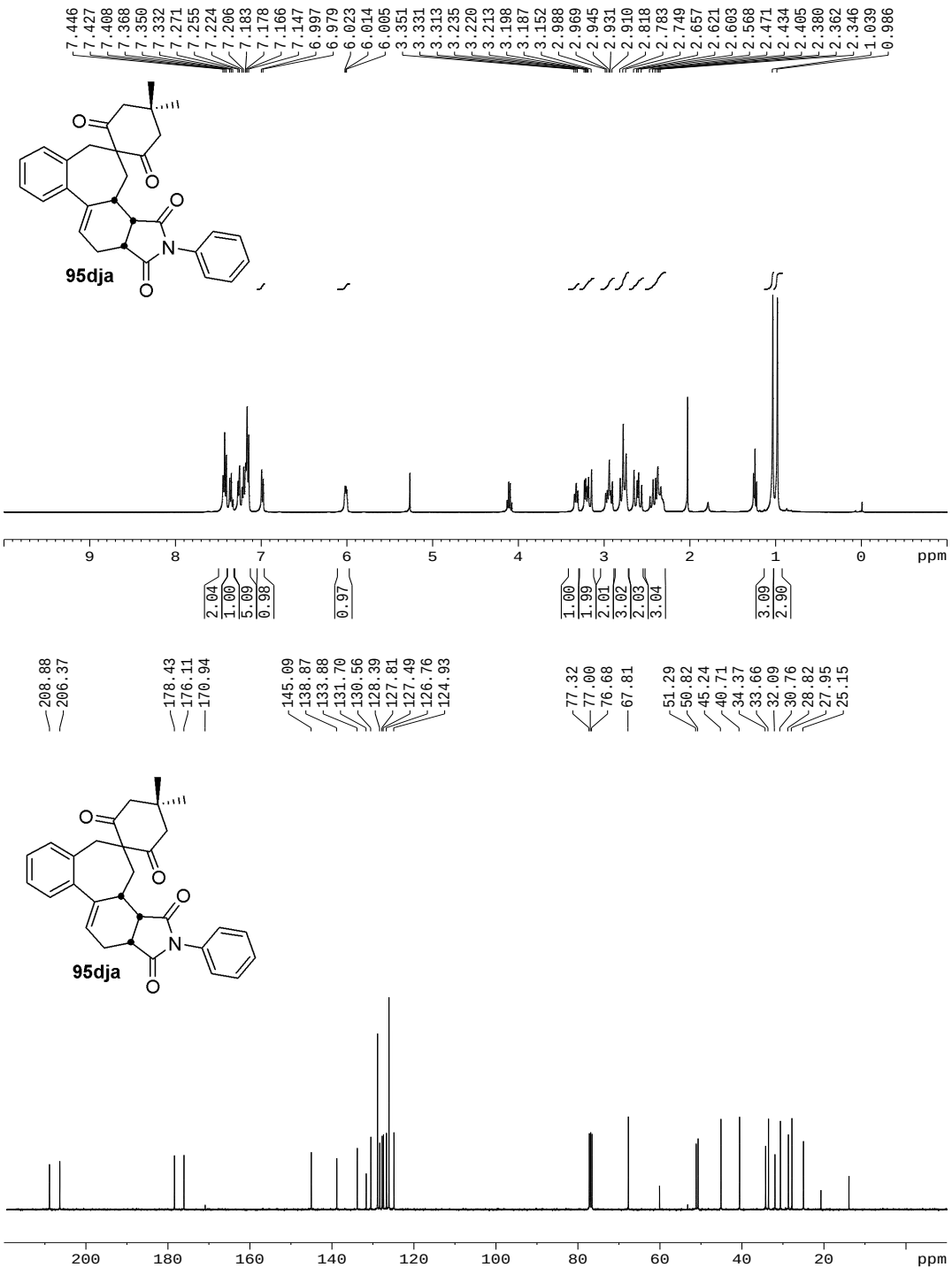


Figure-32: ^{1}H and ^{13}C NMR spectra of the product **95dja**

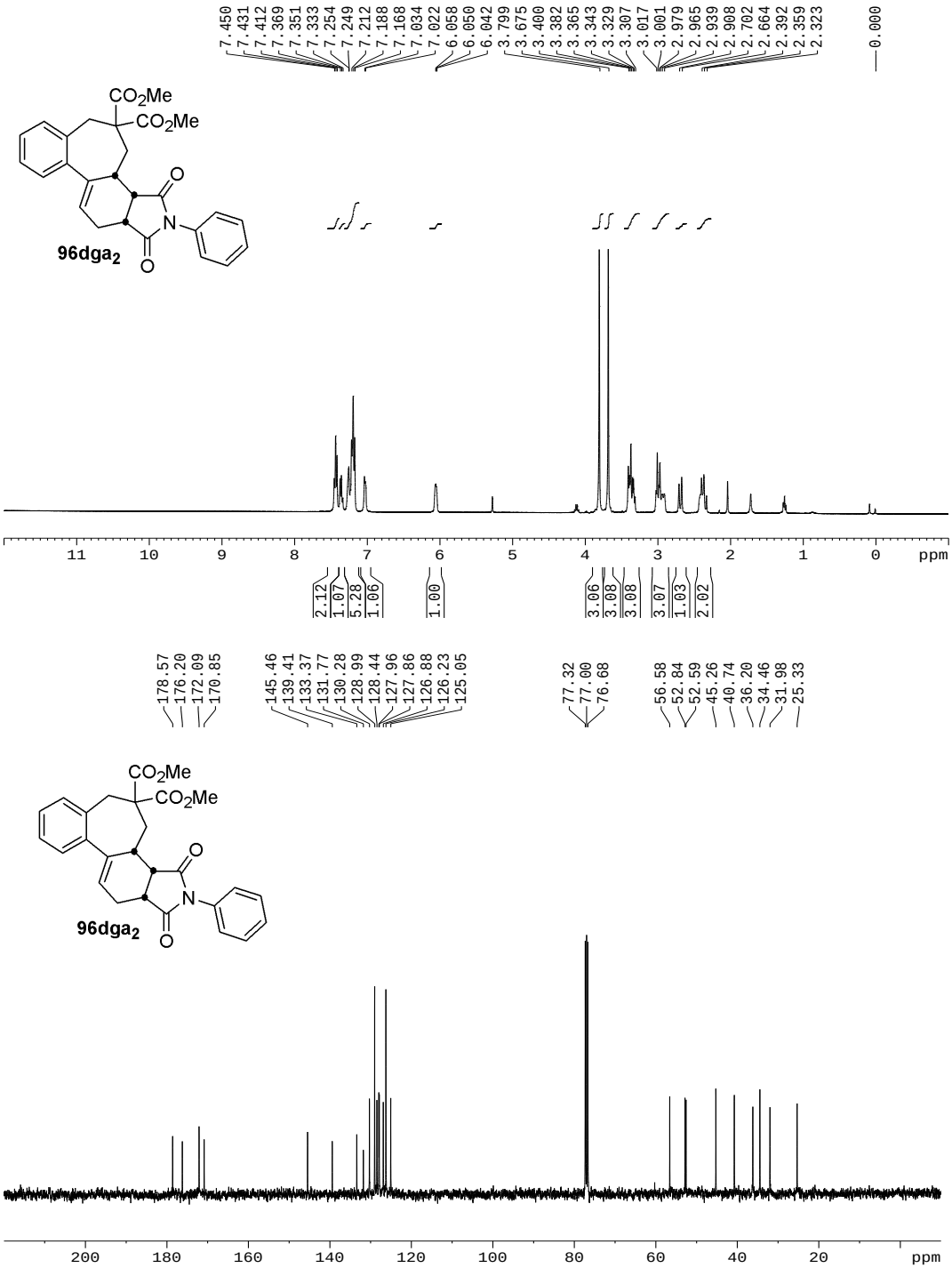


Figure-33: ^{1}H and ^{13}C NMR spectra of the product **96dga$_2$**

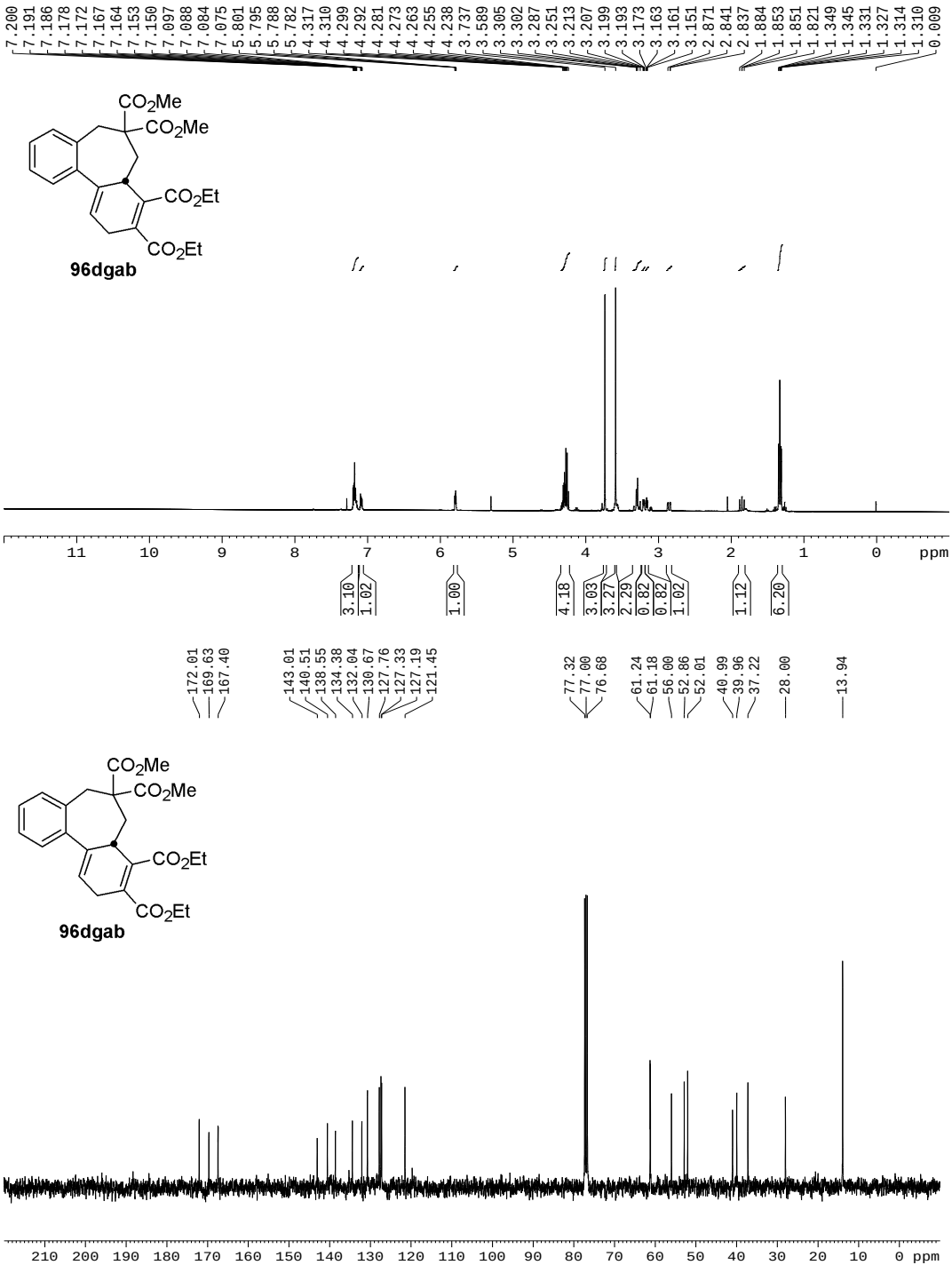


Figure-34: ^{1}H and ^{13}C NMR spectra of the product **96dgab**

In a similar manner, 2-ethynyl-benzaldehyde **5d** was converted into highly functionalized spiro tetra-cyclic product **95djb** in stereospecific manner with 42% overall yield through a sequence of amino acid-/self-/K_2CO_3-catalyzed cascade TCRA/*C*-A, [Ru]-promoted enyne-RCM followed by heat-promoted Diels-Alder reaction with diethyl acetylenedicarboxylate **94b** in one-pot as shown in Table 16, entry 4 and generality of this two-step sequential MCC reactions was further confirmed by two more examples using different CH-acids **20** and dienophile **94b** to furnish the expected highly functionalized tri-cyclic *endo*-product **96dgab** in 54.0% overall yield and *endo*-product **96dgb$_2$** in 57% overall yield with ≤5% de (Table 16, entries 7 and 8).

7.3 CONCLUSION

In summary, a two-step sequential MCC chemistry for the synthesis of highly substituted drug-like carbocycles **92**, **93**, **95** and **96** from simple starting materials *via* TCRA/*C*-A, TCRA/A/K/E/*C*-A, enyne-RCM and Diels-Alder reactions was developed. The MCC reactions proceed in good yields with high selectivity using proline-/self-/K_2CO_3-/[Ru]-/heat as the catalysts. This two-step sequential MCC method gives an insight into the high-yielding synthesis of functionalized carbocycles and its impact would be remarkable.

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9. EXPERIMENTAL SECTION

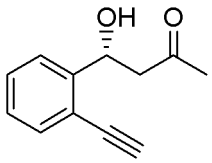
1. General experimental procedures for the asymmetric BLA reactions

1a. *trans*-4-*OH*-L-proline catalyzed BLA reaction of 2-alkynylbenzaldehydes with ketones (Method A): In an ordinary glass vial equipped with a magnetic stirring bar, to 0.3 mmol of 2-ethynylbenzaldehyde **5d** was added 2.4 mL of solvent, followed by the addition of the catalyst *trans*-4-*OH*-L-proline **2j** (0.06 mmol, 20 mol-%, 6.9 mg). After stirring the reaction mixture at 25 °C for 2–3 min, ketone **6** was added and the reaction mixture was allowed to stir at the same temperature for 24–72 h. The crude reaction mixture was worked up with aqueous NH_4Cl solution and the aqueous layer was extracted with ethylacetate (2 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure BLA products **7** were obtained by column chromatography (silica gel, mixture of hexane/ ethylacetate).

1b. Prolinamide 2n catalyzed BLA reaction of 2-alkynylbenzaldehydes with ketone (Method B): In a 10 mL round bottomed flask equipped with a magnetic stirring bar, to the prolinamide catalyst **2n** (10 mol-%) was added $PhCO_2H$ (10 mol-%). The flask was cooled to –35 °C and then ketone **6** (1 ml, 0.3 M) was added to it. After stirring the reaction mixture at –35 °C for 0.5 h, 2-ethynylbenzaldehyde **5d** (0.3 mmol) was added to it and stirring was continued at the same temperature for 24–60 h. The crude reaction mixture was worked up with aqueous NH_4Cl solution and the aqueous layer was extracted with ethylacetate (2 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure BLA products **7** and double-aldol addition products **57** were obtained by column chromatography (silica gel, mixture of hexane/ ethylacetate).

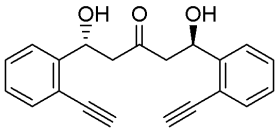
(*R*)-4-(2-Ethynyl-phenyl)-4-hydroxy-butan-2-one (7da): Prepared following the method **A** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC

using a Daicel Chiralcel OD-H column (hexane/2-propanol = 92:8, flow rate 1.0 mL/min, λ= 254 nm), t_R = 8.56 min (minor), t_R = 9.71 min (major). **$[\alpha]_D^{25}$ = + 31.10°** (*c* = 0.28 g/100 mL, $CHCl_3$,**73% *ee***); IR (Neat): ν_{max} 3448, 3286 (O-H), 2925, 1709 (*C*=O), 1447, 1362, 1264, 1165, 1105, 1065, 763, 666, 651 and 625 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.58 (1H, d, *J* = 8.0 Hz), 7.46 (1H, dd, *J* = 7.6, 1.2 Hz), 7.37 (1H, dt, *J* = 7.6, 1.2 Hz), 7.22 (1H, dt, *J* = 7.6, 1.2 Hz)[Ar-*H*]; 5.57 (1H, dd, *J* = 9.6, 2.0 Hz, C*H*OH), 3.61 (1H, br s, O*H*), 3.34 (1H, s, C≡C*H*), 3.00 (1H, dd, *J* = 17.2, 2.4 Hz, COCH_2), 2.72 (1H, dd, *J* =17.6, 9.6 Hz, COCH_2), 2.19 (3H, s, COCH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 209.1 (C, *C*=O), 145.1 (C), 132.7 (CH), 129.3 (CH), 127.1 (CH), 125.2 (CH), 118.8 (C), 82.6 (CH, Ar-C≡*C*H), 81.0 (C, Ar-*C*≡CH), 67.6 (CH, *C*HOH), 50.8 (CH_2, CO*C*H_2), 30.4 (CH_3, CO*C*H_3); LRMS m/z 189.10 (M+1), calcd. for $C_{12}H_{12}O_2$ 188.0837; Anal. calcd. for $C_{12}H_{12}O_2$ (188.0837); C, 76.57; H, 6.43. Found: C, 76.48; H, 6.51%.



7da

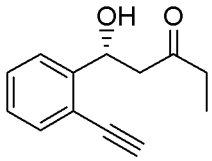
(*R*,*R*)-1,5-Bis-(2-ethynyl-phenyl)-1,5-dihydroxy-pentan-3-one (**57da**): Prepared following method **B**, purified by column chromatography using EtOAc/hexane and isolated as gummy liquid. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 92:8, flow rate 1.0 mL/min, λ= 254 nm), t_R = 20.10 min (minor), t_R = 22.95 min (major). **$[\alpha]_D^{25}$ = +122.96°** (*c* = 0.13 g/100 mL, $CHCl_3$, **>99% *ee***); IR (Neat): ν_{max} 3285 (O-H), 1708 (*C*=O), 1479, 1363, 1316, 1204, 1105, 1059, 763, 685, 650 and 612 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.59 (2H, d, *J* = 8.0 Hz), 7.47 (2H, d, *J* = 7.2 Hz), 7.39 (2H, t, *J* = 7.6 Hz), 7.24 (2H, t, *J* = 7.6 Hz)[Ar-*H*]; 5.64 (2H, d, *J* = 9.2 Hz, 2 x C*H*OH), 3.42 (2H, br s, 2 x O*H*), 3.34 (2H, s, 2 x C≡C*H*), 3.02 (2H, dd, *J* = 16.8, 2.0 Hz, 2 x COCH_2), 2.82 (2H, dd, *J* =17.2, 10.0 Hz, 2 x COCH_2); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 211.0 (C, *C*=O), 145.0 (2 x C), 132.9 (2 x CH), 129.4 (2 x CH), 127.3 (2 x CH), 125.2 (2 x CH), 118.9 (2 x C), 82.9 (2 x CH, 2 x Ar-C≡*C*H), 81.0 (2 x C, 2 x Ar-*C*≡CH), 67.8 (2 x CH, 2 x *C*HOH), 50.6 (2 x CH_2, 2 x CO*C*H_2); LRMS m/z 317.00 (M^+-1), calcd. for



57da

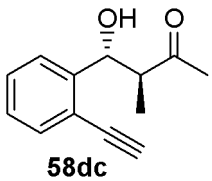
$C_{21}H_{18}O_3$ 318.1256; Anal. calcd. for $C_{21}H_{18}O_3$ (318.1256); C, 79.22; H, 5.70. Found: C, 79.32; H, 5.65%.

(*R*)-1-(2-Ethynyl-phenyl)-1-hydroxy-pentan-3-one (7dc): Prepared following the method **B**, purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 94:6, flow rate 1.0 mL/min, λ= 254 nm), t_R = 9.22 min (major), t_R = 10.44 min (minor). **$[\alpha]_D^{25}$ = + 109.68°** (*c* = 0.43 g/100 mL, $CHCl_3$, **98.6 % *ee***); IR (Neat): ν_{max} 3449, 3291 (O-H), 3069, 2978, 2939, 2102, 1712 (*C*=O), 1448, 1408, 1373, 1311, 1203, 1113, 1070 and 761 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.59 (1H, br dd, *J* = 8.0, 0.5 Hz), 7.47 (1H, dd, *J* = 7.6, 1.2 Hz), 7.39 (1H, dt, *J* = 7.6, 1.3 Hz), 7.23 (1H, dt, *J* = 7.5, 1.3 Hz)[Ar-*H*]; 5.58 (1H, d, *J* = 9.2 Hz, C*H*OH), 3.63 (1H, br s, O*H*), 3.33 (1H, s, Ar-C≡C*H*), 3.00 (1H, dd, *J* = 17.4, 2.0 Hz, COCH_2), 2.69 (1H, dd, *J* =17.6, 10.0 Hz, COCH_2), 2.56–2.40 (2H, m, COC$H_2$$CH_3$), 1.08 (3H, t, *J* = 7.3 Hz, $COCH_2CH_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 212.2 (C, *C*=O), 145.2 (C), 132.8 (CH), 129.4 (CH), 127.1 (CH), 125.2 (CH), 118.8 (C), 82.6 (CH, Ar-C≡*C*H), 81.1 (C, Ar-*C*≡CH), 67.9 (CH, *C*HOH), 49.4 (CH_2, CO*C*H_2), 36.6 (CH_2, CO*C*H_2CH_3), 7.5 (CH_3, $COCH_2CH_3$); LRMS m/z 203.00 (M+1), calcd. for $C_{13}H_{14}O_2$ 202.0994; Anal. calcd. for $C_{13}H_{14}O_2$ (202.0994); C, 77.20, H, 6.98; Found: C, 77.35; H, 6.87%.



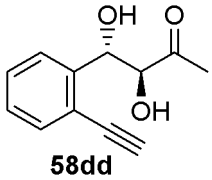
7dc

(*3S,4R*)-4-(2-Ethynyl-phenyl)-4-hydroxy-3-methyl-butan-2-one (58dc): Prepared following method **B**, purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 94:6, flow rate 1.0 mL/min, λ= 254 nm), t_R = 10.91 min (major), t_R = 12.43 min (minor). **$[\alpha]_D^{25}$ = + 30.88°** (*c* = 0.13 g/100 mL, $CHCl_3$, **99.6 % *ee***); IR (Neat): ν_{max} 3430, 3295 (O-H), 3065, 2975, 2934, 2104, 1707 (C=O), 1481, 1456, 1360, 1242, 1170, 1100, 1051, 1019, 955, 912, 833 and 764 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.49 (1H, dd, *J* = 8.0, 1.2 Hz), 7.47–7.45 (1H,



58dc

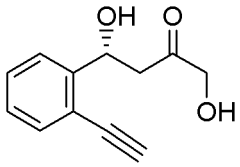
m), 7.39 (1H, dt, *J* = 8.0, 1.2 Hz), 7.25 (1H, dt, *J* = 7.6, 1.2 Hz)[Ar-*H*]; 5.29 (1H, dd, *J* = 7.2, 3.4 Hz, C*H*OH), 3.35 (1H, s, Ar-C≡C*H*), 3.30 (1H, br s, O*H*), 3.09 (1H, quintet, *J* = 7.6 Hz, COC*H*CH_3), 2.16 (3H, s, COCH_3), 1.06 (3H, d, *J* = 7.2 Hz, COCHCH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 213.6 (C, *C*=O), 144.4 (C), 132.9 (CH), 129.3 (CH), 127.5 (CH), 126.2 (CH), 120.3 (C), 82.4 (CH, Ar-C≡*C*H), 81.5 (C, Ar-*C*≡CH), 73.7 (CH, *C*HOH), 53.0 (CH, CO*C*HCH_3), 30.0 (CH_3, CO*C*H_3), 14.0 (CH_3, COCH*C*H_3); LRMS m/z 203.05 (M+1), calcd. for $C_{13}H_{14}O_2$ 202.0994; Anal. calcd. for $C_{13}H_{14}O_2$ (202.0994); C, 77.20, H, 6.98; Found: C, 77.38; H, 7.05%.



58dd

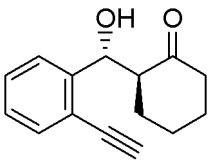
(*3S,4R*)-4-(2-Ethynyl-phenyl)-3,4-dihydroxy-butan-2-one (58dd): Prepared following method **B**, purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 94:6, flow rate 1.0 mL/min, λ= 254 nm), t_R(*syn*) = 18.46 min (major), t_R(*syn*) = 23.66 min (minor); t_R(*anti*) = 26.86 min (major), t_R(*anti*) = 29.22 min (minor). IR (Neat): ν_{max} 3418, 3283 (O-H), 3067, 2926, 2099, 1960, 1715 (C=O), 1622, 1399, 1360, 1254, 1096, 1053 and 762 cm^{-1}; **^{1}H NMR ($CDCl_3$, 2.5:1 mixture of *anti:syn* diastereomers)** δ 7.59 (1H, d, *J* = 8.0 Hz), 7.54–7.50 (3H, m), 7.44–7.38 (2H, m), 7.31–7.26 (2H, m)[Ar-*H*]; 5.60 (1H, s, ArC*H*OH), 5.42 (1H, d, *J* = 4.0 Hz, ArC*H*OH), 4.75 (1H, d, *J* = 3.2 Hz, COC*H*OH), 4.52 (1H, s, COC*H*OH), 3.89 (1H, br. s, OH), 3.74 (1H, br. s, OH), 3.45 (1H, s, Ar-C≡C*H*), 3.42 (1H, s, Ar-C≡C*H*), 3.16 (1H, br. s, OH), 3.00 (1H, br. s, OH), 2.37 (3H, s, COCH_3), 1.88 (3H, s, COCH_3); **^{13}C NMR ($CDCl_3$, DEPT-135, 2.5:1 mixture of *anti:syn* diastereomers)** δ 208.1 (C, *C*=O), 207.4 (C, C=O), 142.8 (C), 141.3 (C), 133.2 (CH), 132.9 (CH), 129.3 (2 x CH), 127.9 (CH), 127.6 (CH), 126.3 (CH), 126.0 (CH), 119.9 (C), 119.0 (C), 83.3 (CH, Ar-C≡*C*H), 83.2 (CH, Ar-C≡*C*H), 81.5 (C, Ar-*C*≡CH), 81.1 (C, Ar-*C*≡CH), 79.7 (CH, Ar*C*HOH), 79.4 (CH, Ar*C*HOH), 73.2 (CH, CO*C*HOH), 71.1 (CH, CO*C*HOH), 27.9 (CH_3, CO*C*H_3), 25.3 (CH_3, CO*C*H_3); LRMS m/z 205.20 (M+1), calcd. for $C_{12}H_{12}O_3$ 204.0786; Anal. calcd. for $C_{12}H_{12}O_3$ (204.0786); C, 70.57, H, 5.92; Found: C, 70.42; H, 5.85%.

(*R*)-4-(2-Ethynyl-phenyl)-1,4-dihydroxy-butan-2-one (7dd): Prepared following method **B**, purified by column chromatography using EtOAc/hexane and isolated as liquid. IR (Neat): ν_{max} 3397 (O-H), 3283, 3073, 2926, 2859, 1715 (C=O), 1622, 1449, 1389, 1263, 1161, 1069 and 762 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.63 (1H, d, *J* = 7.6 Hz), 7.50 (1H, d, *J* = 7.6 Hz), 7.40 (1H, dt, *J* = 7.6, 1.1 Hz), 7.28 (1H, dt, *J* = 7.6, 1.1 Hz) [Ar-*H*]; 5.65 (1H, dd, *J* = 9.6, 2.4 Hz), 4.33 (2H, ABq, *J* = 19.2 Hz), 3.37 (1H, s, Ar-C≡C*H*), 2.95 (1H, dd, *J* = 16.4, 2.8 Hz), 2.79 (1H, dd, *J* = 16.4, 9.6 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 209.3 (C, *C*=O), 144.8 (C), 133.0 (CH), 129.5 (CH), 128.5 (CH), 125.1 (CH), 118.9 (C), 83.1 (CH, Ar-C≡*C*H), 81.0 (C, Ar-*C*≡CH), 68.8 (CH_2, CO*C*H_2OH), 67.9 (CH, Ar*C*HOH), 46.1 (CH_2, CO*C*H_2); LRMS m/z 205.20 (M+1), calcd. for $C_{12}H_{12}O_3$ 204.0786; Anal. calcd. for $C_{12}H_{12}O_3$ (204.0786); C, 70.57, H, 5.92; Found: C, 70.45; H, 5.86%.



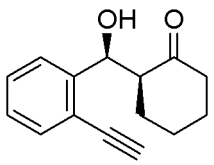
7dd

(*2S,1'R*)-2-[(2-Ethynyl-phenyl)-hydroxy-methyl]-cyclohexanone (*anti*–7db): Prepared following method **B**, purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 92:8, flow rate 1.0 mL/min, λ= 254 nm), t_R = 8.42 min (major), t_R = 9.87 min (minor). **$[\alpha]_D^{25}$ = +41.60°** (*c* = 0.14 g/100 mL, $CHCl_3$, **96.2% *ee***); IR (Neat): ν_{max} 3520, 3442, 3285 (O-H), 2940, 2868, 1694 (C=O), 1445, 1409, 1311, 1230, 1128, 1037, 1017, 763, 652 and 625 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.52 (1H, d, *J* = 8.0 Hz), 7.47 (1H, d, *J* = 8.0 Hz), 7.39 (1H, t, *J* = 7.6 Hz), 7.24 (1H, t, *J* = 7.6 Hz)[Ar-*H*]; 5.39 (1H, d, *J* = 8.4 Hz, C*H*OH), 4.04 (1H, br s, O*H*), 3.27 (1H, s, Ar-C≡C*H*), 2.73–2.66 (1H, m), 2.46 (1H, d, *J* = 13.2 Hz), 2.34 (1H, dt, *J* = 13.2, 6.0 Hz), 2.09–2.04 (1H, m), 1.82–1.79 (1H, m), 1.74–1.66 (1H, m), 1.61–1.51 (3H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 215.4 (C, *C*=O), 143.7 (C), 132.5 (CH), 129.3 (CH), 127.3 (CH), 126.4 (CH), 120.9 (C), 81.8 (CH, Ar-C≡*C*H), 81.7 (C, Ar-*C*≡CH), 71.6 (CH, *C*HOH), 57.7 (CH, CO*C*H-), 42.6 (CH_2), 30.4 (CH_2), 27.7 (CH_2),



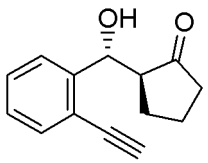
anti–**7db**

24.8 (CH_2); LRMS m/z 228.20 (M^+), calcd. for $C_{15}H_{16}O_2$ 228.1150; Anal. calcd. for $C_{15}H_{16}O_2$ (228.1150); C, 78.92, H, 7.06; Found: C, 78.81; H, 7.15%.



syn–**7db**

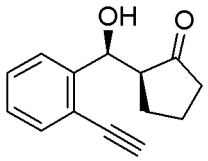
(*2S,1'S*)-2-[(2-Ethynyl-phenyl)-hydroxy-methyl]-cyclohexanone (*syn*–7db): Prepared following method **B**, purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AS-H column (hexane/2-propanol = 94:6, flow rate 1.0 mL/min, λ= 254 nm), t_R = 10.65 min (minor), t_R = 11.98 min (major). **$[\alpha]_D^{25}$ = +108.79°** (*c* = 0.06 g/100 mL, $CHCl_3$, **91.4% *ee***); IR (Neat): ν_{max} 3459, 3291 (O-H), 3061, 2940, 2866, 1703 (C=O), 1605, 1449, 1308, 1235, 1130, 1065, 1032, 978, 887 and 762 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.55 (1H, d, *J* = 7.8 Hz), 7.46 (1H, d, *J* = 7.6 Hz), 7.37 (1H, t, *J* = 7.6 Hz), 7.22 (1H, t, *J* = 7.5 Hz)[Ar-*H*]; 5.80 (1H, br s, C*H*OH), 3.29 (1H, s, Ar-C≡C*H*), 3.19 (1H, br s, O*H*), 2.88 (1H, dd, *J* = 12.6, 5.2 Hz), 2.47–2.35 (2H, m), 2.10–2.04 (1H, m), 1.84–1.49 (5H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 214.8 (C, *C*=O), 143.8 (C), 132.7 (CH), 128.7 (CH), 126.7 (CH), 126.5 (CH), 118.5 (C), 82.6 (CH, Ar-C≡*C*H), 81.2 (C, Ar-*C*≡CH), 68.7 (CH, *C*HOH), 54.6 (CH, CO*C*H), 42.5 (CH_2), 27.9 (CH_2), 25.9 (CH_2), 24.8 (CH_2); LRMS m/z 228.70 (M+1), calcd. for $C_{15}H_{16}O_2$ 228.1150; Anal. calcd. for $C_{15}H_{16}O_2$ (228.1150); C, 78.92, H, 7.06; Found: C, 78.82; H, 6.95%.



anti–**7de**

(*2S,1'R*)-2-[(2-Ethynyl-phenyl)-hydroxy-methyl]-cyclopentanone (*anti*–7de): Prepared following method **B**, purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ= 254 nm), t_R = 10.51 min (major), t_R = 12.42 min (minor). **$[\alpha]_D^{25}$ = –6.69°** (*c* = 0.48g/100 mL, $CHCl_3$, **94.6% *ee***); IR (Neat): ν_{max} 3281 (O-H), 3065, 2967, 2882, 2102, 1937, 1728 (C=O), 1622, 1402, 1159, 1026, 841 and 766 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.56 (1H, dd, *J* = 8.0, 0.8 Hz), 7.48 (1H, dd, *J* = 8.0, 1.2 Hz), 7.41 (1H, dt, *J*

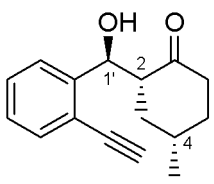
= 8.0, 1.2 Hz), 7.25 (1H, dt, *J* = 7.6, 1.2 Hz)[Ar-*H*]; 5.33 (1H, d, *J* = 9.6 Hz, C*H*OH), 4.58 (1H, br s, O*H*), 3.27 (1H, s, Ar-C≡C*H*), 2.50–2.40 (2H, m), 2.36–2.26 (1H, m), 2.05–1.95 (1H, m), 1.80–1.65 (3H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 223.2 (C, *C*=O), 143.8 (C), 132.8 (CH), 129.5 (CH), 127.6 (CH), 126.5 (CH), 120.4 (C), 81.9 (C, Ar-*C*≡CH), 81.8 (CH, Ar-C≡*C*H), 71.8 (CH, *C*HOH), 55.7 (CH), 38.7 (CH_2), 26.4 (CH_2), 20.5 (CH_2); LRMS m/z 213.10 (M-1), calcd. for $C_{14}H_{14}O_2$ 214.0994; Anal. calcd. for $C_{14}H_{14}O_2$ (214.0994); C, 78.48, H, 6.59; Found: C, 78.32; H, 6.65%.



syn–**7de**

(*2S,1'S*)-2-[(2-Ethynyl-phenyl)-hydroxy-methyl]-cyclopentanone (*syn*–7de): Prepared following method **B,** purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AS-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ= 254 nm), t_R = 11.52 min. , t_R = 14.61 min., **0% *ee*** ; IR (Neat): ν_{max} 3443, 3291 (O-H), 3065, 2965, 2882, 1736 (C=O), 1622, 1478, 1449, 1402, 1337, 1269, 1204, 1157, 1107, 1026, 968, 883, 841 and 762 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.57 (1H, d, *J* = 7.6 Hz), 7.47 (1H, dd, *J* = 7.6, 1.2 Hz), 7.39 (1H, dt, *J* = 7.6, 0.8 Hz), 7.24 (1H, dt, *J* = 7.6, 1.2 Hz)[Ar-*H*]; 5.78 (1H, s, C*H*OH), 3.36 (1H, s, Ar-C≡C*H*), 2.77–2.72 (1H, m), 2.41–2.33 (2H, m), 2.20–2.10 (1H, m), 2.03–1.95 (2H, m), 1.76–1.65 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 220.1 (C, *C*=O), 145.0 (C), 132.7 (CH), 129.0 (CH), 127.0 (CH), 125.5 (CH), 118.8 (C), 83.0 (CH, Ar-C≡*C*H), 80.9 (C, Ar-*C*≡CH), 69.2 (CH, *C*HOH), 54.3 (CH), 39.0 (CH_2), 22.6 (CH_2), 20.3 (CH_2); LRMS m/z 213.10 (M-1), calcd. for $C_{14}H_{14}O_2$ 214.0994; Anal. calcd. for $C_{14}H_{14}O_2$ (214.0994); C, 78.48, H, 6.59; Found: C, 78.36; H, 6.51%.

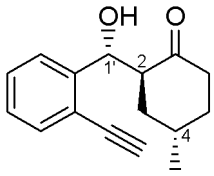
***(2R,4S,1'S)*-2-[(2-Ethynyl-phenyl)-hydroxy-methyl]-4-methyl-cyclohexanone**



(*2R, 4S, 1'S*)–7df

[*(2R,4S,1'S)*–7df]: Prepared following method **B**, purified by column chromatography using EtOAc/hexane and isolated as a yellow liquid. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OJ-H column

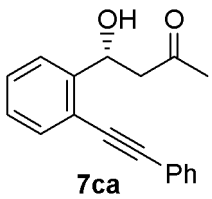
(hexane/2-propanol = 96:4, flow rate 1.0 mL/min, λ= 254 nm), t_R = 17.37 min (minor), t_R = 18.55 min (major). **$[\alpha]_D^{25}$ = –8.03°** (*c* = 0.15 g/100 mL, $CHCl_3$, >99% ***de*** and 81% ***ee***); IR (Neat): ν_{max} 3443, 3267 (O-H), 2961, 2876, 2830, 1708 (C=O), 1452, 1379, 1327, 1187, 1125, 1099, 1038, 951 and 763 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.51–7.47 (2H, m), 7.39 (1H, t, *J* = 7.6 Hz), 7.27–7.23 (1H, m)[Ar-*H*]; 5.40 (1H, d, *J* = 8.4 Hz, C*H*OH), 3.71 (1H, br. s, OH), 3.30 (1H, s, Ar-C≡C*H*), 2.86 (1H, dd, *J* = 8.8, 2.8 Hz), 2.53–2.40 (2H, m), 2.17–2.10 (1H, m), 2.00–1.92 (1H, m), 1.76–1.64 (2H, m), 1.40–1.34 (1H, m), 1.01 (3H, d, *J* = 6.8 Hz, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 215.3 (C, *C*=O), 144.0 (C), 132.7 (CH), 129.4 (CH), 127.5 (CH), 126.4 (CH), 120.7 (C), 81.9 (CH, Ar-C≡*C*H), 81.7 (C, Ar-*C*≡CH), 72.0 (CH, *C*HOH), 54.0 (CH), 38.4 (CH_2), 36.1 (CH_2), 33.6 (CH_2), 26.9 (CH), 18.7 (CH_3); LRMS m/z 243.10 (M+1), calcd. for $C_{16}H_{18}O_2$ 242.1307; Anal. calcd. for $C_{16}H_{18}O_2$ (242.1307); C, 79.31, H, 7.49; Found: C, 79.45; H, 7.41%.



(2S, 4S, 1'R)-7df

(2S,4S,1'R)*-2-[(2-Ethynyl-phenyl)-hydroxy-methyl]-4-methyl-cyclohexanone [*(2S,4S,1'R)*–7df]:** Prepared following method **A**, purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 94:6, flow rate 1.0 mL/min, λ= 254 nm), t_R = 8.67 min (minor), t_R = 11.43 min (major). **$[\alpha]_D^{25}$ = –172.73°** (*c* = 0.14 g/100 mL, $CHCl_3$, 82% ***ee); IR (Neat): ν_{max} 3415, 3298 (O-H), 3279, 2955, 2874, 1704 (C=O), 1451, 1306, 1258, 1220, 1198, 1121 1077, 1021 and 763 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.53 (1H, d, *J* = 7.6 Hz), 7.47 (1H, dd, *J* = 7.6, 1.2 Hz), 7.38 (1H, dt, *J* = 7.6, 1.2 Hz), 7.23 (1H, dt, *J* = 7.6, 1.2 Hz)[Ar-*H*]; 5.79 (1H, s, C*H*OH), 3.31 (1H, s, Ar-C≡C*H*), 3.14–3.09 (1H, m), 3.03 (1H, d, *J* = 2.4 Hz), 2.59–2.51 (1H, m), 2.38–2.31 (1H, m), 2.13–2.01 (2H, m), 1.95–1.88 (1H, m), 1.79–1.74 (1H, m), 1.35–1.29 (1H, m), 1.03 (3H, d, *J* = 6.8 Hz, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 215.3 (C, *C*=O), 143.7 (C), 132.9 (CH), 128.9 (CH), 126.8 (CH), 126.6 (CH), 118.6 (C), 82.6 (CH, Ar-C≡*C*H), 81.3 (C, Ar-*C*≡CH),

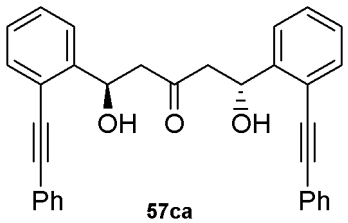
69.2 (CH, *C*HOH), 50.2 (CH), 38.3 (CH_2), 33.1 (CH_2), 31.7 (CH_2), 26.7 (CH), 18.3 (CH_3); LRMS m/z 243.10 (M+1), calcd. for $C_{16}H_{18}O_2$ 242.1307; Anal. calcd. for $C_{16}H_{18}O_2$ (242.1307); C, 79.31, H, 7.49; Found: C, 79.45; H, 7.53%.



7ca

(*R*)-4-Hydroxy-4-(2-phenylethynyl-phenyl)-butan-2-one (7ca): Prepared following method **A,** purified by column chromatography using EtOAc/hexane and isolated as white solid. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralcel AD-H column (hexane/2-propanol = 94:6, flow rate 1.0 mL/min, λ= 254 nm), t_R = 13.52 min (major), t_R = 15.56 min (minor). **$[\alpha]_D^{25}$ = +52.19°** (*c* = 0.54 g/100 mL, $CHCl_3$, **76.2% *ee***); IR (Neat): ν_{max} 3352 (O-H), 2929, 1706 (*C*=O), 1494, 1406, 1365, 1260, 1186, 1164, 1102, 1064, 756, 690 and 664 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.61 (1H, d, *J* = 8.0 Hz), 7.51–7.47 (3H, m), 7.40–7.34 (4H, m), 7.26 (1H, t, *J* = 8.0 Hz)[Ar-*H*]; 5.69 (1H, d, *J* = 8.0 Hz, C*H*OH), 3.48 (1H, br s, O*H*), 3.07 (1H, dd, *J* = 17.6, 1.6 Hz, COCH_2), 2.77 (1H, dd, *J* =17.6, 9.6 Hz, COCH_2), 2.19 (3H, s, COCH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 209.2 (C, *C*=O), 144.5 (C), 132.0 (CH), 131.4 (2 x CH), 128.9 (CH), 128.51 (CH), 128.45 (2 x CH), 127.2 (CH), 125.1 (CH), 122.8 (C), 119.9 (C), 94.9 (C, Ar-C≡*C*Ph), 86.6 (C, Ar-C≡*C*Ph), 68.0 (CH, *C*HOH), 50.9 (CH_2, CO*C*H_2), 30.7 (CH_3, CO*C*H_3); LRMS m/z 263.00 (M-1), calcd. for $C_{18}H_{16}O_2$ 264.1150; Anal. calcd. for $C_{18}H_{16}O_2$ (264.1150); C, 81.79; H, 6.10. Found: C, 81.65; H, 6.22%.

(*R*,*R*)-1,5-Dihydroxy-1,5-bis-(2-phenylethynyl-phenyl)-pentan-3-one (57ca):

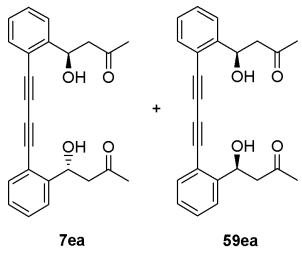


57ca

Prepared following method **B,** purified by column chromatography using EtOAc/hexane and isolated as yellow gummy liquid. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 94:6, flow rate 1.0 mL/min, λ= 254 nm), t_R = 56.27 min (minor), t_R = 61.58 min (major), **>99.9% *ee***. IR (Neat): ν_{max} 3410 (O-H), 3059, 2926, 2216, 1960, 1713 (C=O), 1597, 1493, 1447, 1389, 1267, 1063, 756 and 691 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.58 (4H,

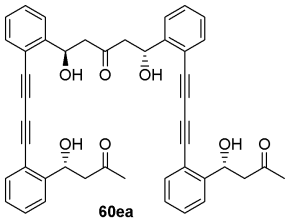
d, *J* = 7.0 Hz), 7.51–7.48 (8H, m), 7.34–7.32 (6H, m)[Ar-*H*]; 5.78 (2H, dd, *J* = 9.9, 2.1 Hz, 2 x C*H*OH), 3.20 (2H, br s, O*H*), 3.09 (2H, dd, *J* = 16.8, 2.4 Hz, COCH_2), 2.86 (2H, dd, *J* =16.8, 9.8 Hz, COCH_2); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 210.8 (C, *C*=O), 144.4 (2 x C), 132.1 (2 x CH), 131.5 (4 x CH), 128.9 (2 x CH), 128.6 (2 x CH), 128.5 (4 x CH), 127.3 (2 x CH), 125.1 (2 x CH), 122.8 (2 x C), 120.0 (2 x C), 95.2 (2 x C, 2 x Ar-*C*≡CPh), 86.5 (2 x C, 2 x Ar-C≡*C*Ph), 68.1 (2 x CH, 2 x *C*HOH), 51.1 (2 x CH_2, 2 x CO*C*H_2); LRMS m/z 471.30 (M^+ +1), calcd. for $C_{33}H_{26}O_3$ 470.1882; Anal. calcd. for $C_{33}H_{26}O_3$ (470.1882); C, 84.23; H, 5.57. Found: C, 84.15; H, 5.63%.

(*R*,*R*)-4-Hydroxy-4-(2-{4-[2-(1-hydroxy-3-oxo-butyl)-phenyl]-buta-1,3-diynyl}-phenyl)-butan-2-one (7ea, major) and (*R*,*S*)-4-Hydroxy-4-(2-{4-[2-(1-hydroxy-3-oxo-butyl)-phenyl]-buta-1,3-diynyl}-phenyl)-butan-2-one (59ea, minor): Prepared following method **B,** purified by column chromatography using EtOAc/hexane and isolated as yellow liquid. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OJ-H column (hexane/2-propanol = 94:6, flow rate 1.0 mL/min, λ= 254 nm), t_R = 44.46 min (minor), t_R = 57.34 min (major). **$[\alpha]_D^{25}$ = +69.49°** (*c* = 0.27 g/100 mL, $CHCl_3$, 21:1 dr, **99.1% *ee***);IR (Neat): ν_{max} 3432 (O-H), 3065, 2920, 2213, 2143, 1715 (C=O), 1711 (C=O), 1476, 1447, 1362, 1233, 1163, 1107, 1067, 955, 887, 818 and 762 cm^{-1}; ^{1}H NMR ($CDCl_3$, **major isomer**) δ 7.61 (2H, d, *J* = 7.8 Hz), 7.51 (2H, d, *J* = 7.2 Hz), 7.41 (2H, dt, *J* = 7.6, 1.0 Hz), 7.25 (2H, dt, *J* = 7.6, 1.2 Hz)[Ar-*H*]; 5.56 (2H, dd, *J* = 9.6, 2.0 Hz, 2 x C*H*OH), 3.69 (2H, br s, 2 x O*H*), 2.99 (2H, dd, *J* = 17.4, 2.4 Hz, COCH_2), 2.76 (2H, dd, *J* =17.4, 9.6 Hz, COCH_2), 2.24 (6H, s, 2 x COCH_3); ^{13}C NMR ($CDCl_3$, DEPT-135, **major isomer**) δ 209.15 (2 x C, 2 x *C*=O), 146.0 (2 x C), 133.23 (2 x CH), 129.9 (2 x CH), 127.3 (2 x CH), 125.5 (2 x CH), 118.42 (2 x C), 80.2 (2 x C), 78.5 (2 x C), 67.8 (2 x CH, 2 x *C*HOH), 50.9 (2 x CH_2, 2 x CO*C*H_2), 30.6 (2 x CH_3, 2 x CO*C*H_3); LRMS m/z 375.30 (M+1), calcd. for $C_{24}H_{22}O_4$ 374.1518; Anal. calcd. for $C_{24}H_{22}O_4$ (374.1518); C, 76.99; H, 5.92. Found: C, 76.85; H, 5.98%.



7ea 59ea

1,5-Dihydroxy-1,5-bis-(2-{4-[2-(1-hydroxy-3-oxo-butyl)-phenyl]-buta-1,3-diynyl}-phenyl)-pentan-3-one (60ea): Prepared following method **B,** purified by column chromatography using EtOAc/hexane and isolated as yellow liquid. IR (Neat): ν_{max} 3401 (O-H), 3059, 2957, 2928, 2866, 2212, 1964, 1713 (C=O), 1597, 1449, 1362, 1263, 1190, 1063, 891, 760 and 704 cm^{-1}; LRMS m/z 689.00 (M-1), calcd. for $C_{45}H_{38}O_7$ 690.2618; HRMS m/z 713.2535 ($M+Na^+$), calcd. for $C_{45}H_{38}O_7Na$ 713.2516. Anal. calcd. for $C_{45}H_{38}O_7$ (690.2618); C, 78.24; H, 5.54. Found: C, 78.15; H, 5.59%.

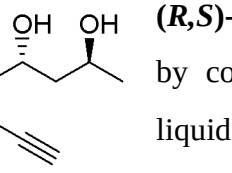


60ea

(*R,R*)-1-(2-Ethynyl-phenyl)-butane-1,3-diol (*syn*–61da): Purified by column chromatography using EtOAc/hexane and isolated as liquid. IR (Neat): ν_{max} 3293 (O-H), 3063, 2973, 2903, 2103, 1698, 1447, 1373, 1318, 1208, 1130, 1069, 932, 847 and 763 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.57 (1H, d, *J* = 8.4 Hz), 7.46 (1H, d, *J* = 7.2 Hz), 7.38 (1H, t, *J* = 7.2 Hz), 7.22 (1H, t, *J* = 7.2 Hz)[Ar-*H*]; 5.38 (1H, d, *J* = 10.0 Hz, C*H*OH), 4.21–4.11 (1H, m), 3.79 (1H, br s, O*H*), 3.43 (1H, br s, OH), 3.32 (1H, s, Ar-C≡C*H*), 1.92–1.85 (1H, m), 1.76–1.70 (1H, m), 1.21 (3H, d, *J* = 6.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 146.8 (C), 132.7 (CH), 129.4 (CH), 127.0 (CH), 125.2 (CH), 118.9 (C), 82.2 (CH, Ar-C≡*C*H), 81.3 (C, Ar-*C*≡CH), 72.7 (CH, *C*HOH), 69.0 (CH, *C*HOH), 45.9 (CH_2), 23.9 (CH_3); LRMS m/z 188.95 (M-1), calcd. for $C_{12}H_{14}O_2$ 190.0994; Anal. calcd. for $C_{12}H_{14}O_2$ (190.0994); C, 76.57; H, 6.43. Found: C, 75.68; H, 7.51%.

syn–**61da**

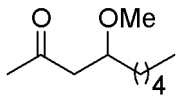
(*R,S*)-1-(2-Ethynyl-phenyl)-butane-1,3-diol (*anti*–61da): Purified by column chromatography using EtOAc/hexane and isolated as liquid. IR (Neat): ν_{max} 3293 (O-H), 3065, 2971, 2917, 2103, 1644, 1447, 1420, 1377, 1335, 1109, 1071, 974, 937, 866, 814 and 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.61 (1H, d, *J* = 7.2 Hz), 7.47 (1H, d, *J* = 7.6 Hz), 7.39 (1H, t, *J* = 7.2 Hz), 7.23 (1H, t, *J* = 7.2 Hz)[Ar-*H*]; 5.52 (1H, s, C*H*OH), 4.07 (1H, s), 3.43



anti–**61da**

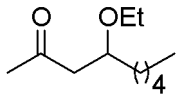
(1H, br s, O*H*), 3.33 (1H, s, Ar-C≡C*H*), 2.53 (1H, br. s, OH), 2.00–1.90 (2H, m), 1.27 (3H, d, *J* = 6.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 146.8 (C), 132.9 (CH), 129.2 (CH), 126.9 (CH), 125.4 (CH), 118.9 (C), 82.4 (CH, Ar-C≡*C*H), 81.3 (C, Ar-*C*≡CH), 69.9 (CH, *C*HOH), 65.9 (CH, *C*HOH), 44.2 (CH_2), 23.3 (CH_3); LRMS m/z 191.15 (M +1), calcd. for $C_{12}H_{14}O_2$ 190.0994; Anal. calcd. for $C_{12}H_{14}O_2$ (190.0994); C, 76.57; H, 6.43. Found: C, 75.61; H, 7.52%.

2. General experimental procedure for the hydroalkoxylation of α,β-unsaturated ketones: In an ordinary glass vial equipped with a magnetic stirring bar, 0.15 mmol of pyrrolidine **2d** and 0.15 mmol of methanesulphonic acid **56e** were taken and the mixture was stirred at 25 °C for 5 minutes. Then alcohol solvent **62** (0.5mL) was added and the mixture was stirred at 25 °C for another 5 minutes. Finally enone **13** (0.5 mmol) was added and the stirring was continued at the same temperature for the time indicated in Tables 4–7. The crude reaction mixture was worked-up with aqueous NH_4Cl or $NaHCO_3$ 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 hydroalkoxylated products **63** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).



63ba

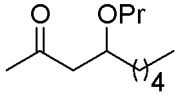
4-Methoxy-nonan-2-one (63ba): Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 2932, 2858, 1718 (C=O), 1460, 1359 and 1095 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.66 (1H, p, *J* = 5.6 Hz, C*H*OMe), 3.31 (3H, s, OC*H*$_3$), 2.66 (1H, dd, *J* = 15.6, 7.6 Hz, C*H*$_2$C=O), 2.45 (1H, dd, *J* = 16.0, 4.8 Hz, C*H*$_2$C=O), 2.17 (3H, s, C*H*$_3$C=O), 1.51–1.25 (8H, m), 0.88 (3H, t, *J* = 7.2 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 207.8 (C, *C*=O), 77.2 (CH, *C*HOMe), 56.8 (CH_3, O*C*H$_3$), 48.2 (CH_2, *C*H$_2$C=O), 33.7 (CH_2), 31.8 (CH_2), 31.1 (CH_3, *C*H$_3$C=O), 24.7 (CH_2), 22.6 (CH_2), 14.0 (CH_3, CH_2CH_3); LRMS (ESI-TOF) m/z 173.15 (M^++1), calcd. for $C_{10}H_{20}O_2$ 172.1463.



63bb

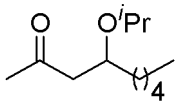
4-Ethoxy-nonan-2-one (63bb): Purified by column chromatography

using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 2930, 2859, 1718 (C=O), 1358 and 1097 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.72 (1H, p, *J* = 6.4 Hz, C*H*OEt), 3.53–3.40 (2H, m, OC*H*$_2$CH$_3$), 2.66 (1H, dd, *J* = 15.6, 7.6 Hz, C*H*$_2$C=O), 2.44 (1H, dd, *J* = 15.6, 4.8 Hz, C*H*$_2$C=O), 2.16 (3H, s, C*H*$_3$C=O), 1.49–1.24 (8H, m, 4 x C*H*$_2$), 1.13 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$), 0.87 (3H, t, *J* = 6.8 Hz, CH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 208.0 (C, *C*=O), 75.7 (CH, *C*HOEt), 64.6 (CH$_2$, O*C*H$_2$CH$_3$), 48.7 (CH$_2$, *C*H$_2$C=O), 34.4 (CH$_2$), 31.8 (CH$_2$), 31.2 (CH$_3$, *C*H$_3$C=O), 24.9 (CH$_2$), 22.5 (CH$_2$), 15.5 (CH$_3$, OCH$_2$*C*H$_3$), 14.0 (CH$_3$, CH$_2$*C*H$_3$); LRMS (ESI-TOF) m/z 187 (M^+ +1), calcd. for $C_{11}H_{22}O_2$ 186.1620.



63bc

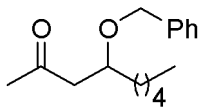
4-Propoxy-nonan-2-one (63bc): Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 2932, 2864, 1718 (C=O), 1462, 1358 and 1093 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.71 (1H, p, *J* = 6.0 Hz, C*H*OPr), 3.41–3.30 (2H, m, OC*H*$_2$CH$_3$), 2.66 (1H, dd, *J* = 15.6, 7.6 Hz, C*H*$_2$C=O), 2.43 (1H, dd, *J* = 15.6, 4.8 Hz, C*H*$_2$C=O), 2.16 (3H, s, C*H*$_3$C=O), 1.54–1.49 (4H, m), 1.31–1.24 (6H, m), 0.89–0.85 (6H, m, 2 x C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 208.1 (C, *C*=O), 75.9 (CH, *C*HOPr), 71.1 (CH$_2$, O*C*H$_2$), 48.6 (CH$_2$, *C*H$_2$C=O), 34.3 (CH$_2$), 31.8 (CH$_2$), 31.2 (CH$_3$, *C*H$_3$C=O), 24.8 (CH$_2$), 23.2 (CH$_2$), 22.5 (CH$_2$), 14.0 (CH$_3$, OCH$_2$CH$_2$*C*H$_3$), 10.6 (CH$_3$); LRMS (ESI-TOF) m/z 201 (M^+ +1), calcd. for $C_{12}H_{24}O_2$ 200.1776.



63bd

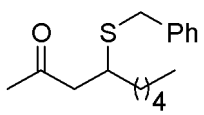
4-Isopropoxy-nonan-2-one (63bd): Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 2930, 2858, 1714 (C=O), 1464, 1365 and 1055 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.78 (1H, p, *J* = 6.4 Hz, C*H*O*i*-Pr), 3.60 [1H, septet, *J* = 6.4 Hz, OC*H*(CH$_3$)$_2$], 2.63 (1H, dd, *J* = 15.2, 6.8 Hz, C*H*$_2$C=O), 2.44 (1H, dd, *J* = 15.2, 5.2 Hz, C*H*$_2$C=O), 2.16 (3H, s, C*H*$_3$C=O), 1.44–1.20 (8H, m, 4 x CH$_2$), 1.09 [6H, dd, *J* = 11.6, 6.4 Hz, OCH(C*H*$_3$)$_2$], 0.87 (3H, t, *J* = 7.2 Hz, CH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 208.3 (C, *C*=O), 73.4 (CH, *C*HO*i*-Pr), 69.9 [CH, O*C*H(CH$_3$)$_2$], 49.2 (CH$_2$, *C*H$_2$C=O), 35.2 (CH$_2$), 31.8 (CH$_2$), 31.5 (CH$_3$, *C*H$_3$C=O), 24.9 (CH$_2$), 22.9

[CH_3, OCH(CH_3)$_2$], 22.64 [CH_3, OCH(CH_3)$_2$], 22.60 (CH_2), 14.0 (CH_3, CH_2CH_3); LRMS (ESI-TOF) m/z 201.25 (M^+ +1), calcd. for $C_{12}H_{24}O_2$ 200.1776.



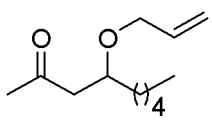
63bf

4-Benzyloxy-nonan-2-one (63bf): Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 2932, 2860, 1716 (C=O), 1454, 1358 and 1095 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35–7.26 (5H, m, aromatic-*H*), 4.51 (2H, dd, *J* = 18.0, 11.2 Hz, OC*H*$_2$Ph), 3.92 (1H, p, *J* = 5.6 Hz, C*H*OCH$_2$Ph), 2.75 (1H, dd, *J* = 16.0, 7.6 Hz, C*H*$_2$C=O), 2.51 (1H, dd, *J* = 15.6, 4.8 Hz, C*H*$_2$C=O), 2.16 (3H, s, C*H*$_3$C=O), 1.65–1.46 (2H, m, C*H*$_2$), 1.38–1.25 (6H, m, 3 x C*H*$_2$), 0.88 (3H, t, *J* = 6.4 Hz, CH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 207.8 (C, *C*=O), 138.5 (C), 128.3 (2 x CH), 127.7 (2 x CH), 127.5 (CH) [Ar-*C*H]; 75.6 (CH, *C*HOCH$_2$Ph), 71.5 (CH_2, O*C*H$_2$Ph), 48.5 (CH_2, *C*H$_2$C=O), 34.2 (CH_2), 31.8 (CH_2), 31.2 (CH_3, *C*H$_3$C=O), 24.8 (CH_2), 22.6 (CH_2), 14.0 (CH_3, CH$_2$*C*H$_3$); LRMS: m/z 249 (M+1), calcd. for $C_{16}H_{24}O_2$ 248.1776.



63'ba

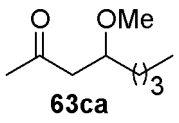
4-Benzylsulfanyl-nonan-2-one (63'ba): Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 2932, 1716 (C=O), 1454, 1359, 1157 and 1070 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.33–7.21 (5H, m, aromatic-*H*), 3.73 (2H, t, *J* = 14.8 Hz, SC*H*$_2$Ph), 3.03 (1H, p, *J* = 6.8 Hz, C*H*SCH$_2$Ph), 2.69–2.56 (2H, m, C*H*$_2$C=O), 2.08 (3H, s, C*H*$_3$C=O), 1.51–1.16 (8H, m, 4 x C*H*$_2$), 0.86 (3H, t, *J* = 7.2 Hz, CH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 206.9 (C, *C*=O), 138.5 (C), 128.9 (2 x CH), 128.4 (2 x CH), 126.9 (CH), 49.6 (CH_2), 40.4 (CH), 35.7 (CH_2), 35.0 (CH_2), 31.5 (CH_2), 30.5 (CH_3, *C*H$_3$C=O), 26.3 (CH_2), 22.5 (CH_2), 14.0 (CH_3); LRMS: m/z 265 ($M^{+\cdot}$+1), calcd. for $C_{16}H_{24}OS$ 264.1548.



63bh

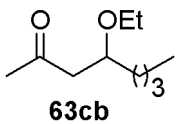
4-Allyloxy-nonan-2-one (63bh): Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 2932, 2860, 1719 (C=O), 1460, 1421, 1358 and 1273 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.91–5.81 (1H, m, olefinic-C*H*), 5.28–5.10 (2H, m, olefinic-C*H*), 3.96 (2H, m, OC*H*$_2$), 3.78 (1H, p, *J* = 5.6 Hz, C*H*OCH$_2$CH=CH$_2$), 2.68 (1H, dd, *J* = 16.0,

7.6 Hz, CH_2C=O), 2.45 (1H, dd, *J* = 15.6, 4.8 Hz, CH_2C=O), 2.16 (3H, s, CH_3C=O), 1.51–1.23 (8H, m), 0.86 (3H, t, *J* = 6.8 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 207.8 (C, *C*=O), 135.0 (CH, *C*H=CH_2), 116.6 (CH_2, CH=*C*H_2), 75.5 (CH), 70.4 (CH_2), 48.6 (CH_2), 34.3 (CH_2), 31.8 (CH_2), 31.2 (CH_3, *C*H_3C=O), 24.8 (CH_2), 22.6 (CH_2), 14.0 (CH_3 , CH_2CH_3); LRMS (ESI-TOF) m/z 199 (M^+ +1), calcd. for $C_{12}H_{22}O_2$ 198.1620.



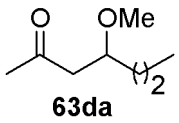
63ca

4-Methoxy-octan-2-one (63ca): Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 2928, 2857, 1730 (C=O) and 1462 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.62 (1H, p, *J* = 7.6 Hz, C*H*OMe), 3.28 (3H, s, OC*H*$_3$), 2.63 (1H, dd, *J* = 16.0, 7.6 Hz, CH_2C=O), 2.42 (1H, dd, *J* = 15.6, 4.8 Hz, CH_2C=O), 2.14 (3H, s, CH_3 C=O), 1.50–1.40 (2H, m, CH_2), 1.29–1.22 (4H, m, 2 x CH_2), 0.86 (3H, t, *J* = 6.8 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 207.7 (C, *C*=O), 77.1 (CH, *C*HOMe), 56.8 (CH_3, O*C*H_3), 48.1 (CH_2, *C*H_2C=O), 33.4 (CH_2), 31.0 (CH_3, *C*H_3C=O), 27.1 (CH_2), 22.7 (CH_2), 13.9 (CH_3, CH_2CH_3); LRMS (ESI-TOF) m/z 159 (M^++1), calcd. for $C_9H_{18}O_2$ 158.1307.



63cb

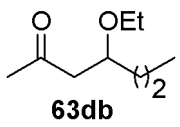
4-Ethoxy-octan-2-one (63cb): Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 2961, 2932, 1717 (C=O), 1358, 1165 and 1097 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.73 (1H, p, *J* = 6.8 Hz, C*H*OEt), 3.54–3.41 (2H, m, OC$H_2$$CH_3$), 2.66 (1H, dd, *J* = 15.6, 7.6 Hz, CH_2C=O), 2.44 (1H, dd, *J* = 15.6, 4.8 Hz, CH_2C=O), 2.17 (3H, s, CH_3C=O), 1.49–1.44 (2H, m, CH_2), 1.34–1.24 (4H, m, 2 x CH_2), 1.23 (3H, t, *J* = 6.8 Hz, OCH_2CH_3), 0.89 (3H, t, *J* = 6.8 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 208.0 (C, *C*=O), 75.7 (CH, *C*HOEt), 64.6 (CH_2, O*C*H_2CH_3), 48.7 (CH_2, *C*H_2C=O), 34.2 (CH_2), 31.2 (CH_3, *C*H_3C=O), 27.4 (CH_2), 22.7 (CH_2), 15.5 (CH_3, OCH_2CH_3), 14.0 (CH_3, CH_2CH_3); LRMS (ESI-TOF) m/z 173.15 (M^++1), calcd. for $C_{10}H_{20}O_2$ 172.1463.



63da

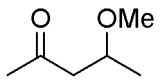
4-Methoxy-heptan-2-one (63da): Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 2930, 2864, 1719 (C=O), 1458, 1358 and 1098 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.66 (1H,

p, *J* = 7.2 Hz, C*H*OMe), 3.31 (3H, s, OC*H*$_3$), 2.65 (1H, dd, *J* = 16.0, 7.6 Hz, C*H*$_2$C=O), 2.44 (1H, dd, *J* = 16.0, 5.2 Hz, C*H*$_2$C=O), 2.16 (3H, s, C*H*$_3$C=O), 1.51–1.24 (4H, m, 2 x C*H*$_2$), 0.91 (3H, t, *J* = 7.2 Hz, CH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$, DEPT–135) δ 207.8 (C, *C*=O), 77.0 (CH, *C*HOMe), 56.9 (CH$_3$, O*C*H$_3$), 48.2 (CH$_2$, *C*H$_2$C=O), 36.0 (CH$_2$), 31.0 (CH$_3$, *C*H$_3$C=O), 18.3 (CH$_2$), 14.1 (CH$_3$, CH$_2$*C*H$_3$); LRMS (ESI-TOF) m/z 145 (M$^+$+1), calcd. for $C_8H_{16}O_2$ 144.1150.



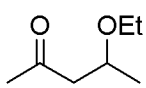
63db

4-Ethoxy-heptan-2-one (63db): Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν$_{max}$ 2926, 1717 (C=O), 1371 and 1097 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 3.73 (1H, p, *J* = 6.8 Hz, C*H*OEt), 3.53–3.41 (2H, m, OC*H*$_2$CH$_3$), 2.66 (1H, dd, *J* = 15.6, 7.6 Hz, C*H*$_2$C=O), 2.44 (1H, dd, *J* = 15.6, 4.8 Hz, C*H*$_2$C=O), 2.16 (3H, s, C*H*$_3$C=O), 1.48–1.30 (4H, m, 2 x C*H*$_2$), 1.13 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$), 0.90 (3H, t, *J* = 6.8 Hz, CH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$, DEPT–135) δ 208.0 (C, *C*=O), 75.5 (CH, *C*HOEt), 64.6 (CH$_2$, O*C*H$_2$CH$_3$), 48.7 (CH$_2$, *C*H$_2$C=O), 36.7 (CH$_2$), 31.2 (CH$_3$, *C*H$_3$C=O), 18.5 (CH$_2$), 15.5 (CH$_3$, OCH$_2$*C*H$_3$), 14.1 (CH$_3$, CH$_2$*C*H$_3$); LRMS (ESI-TOF) m/z 157.05 (M$^+$+1), calcd. for $C_9H_{18}O_2$ 158.1307.



63ea

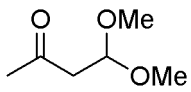
4-Methoxy-pentan-2-one (63ea): Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν$_{max}$ 2930, 1717 (C=O), 1454 and 1175 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 3.76 (1H, sextet, *J* = 6.4 Hz, C*H*OMe), 3.28 (3H, s, OC*H*$_3$), 2.68 (1H, dd, *J* = 16.0, 7.2Hz, C*H*$_2$C=O), 2.40 (1H, dd, *J* = 15.6, 5.2 Hz, C*H*$_2$C=O), 2.14 (3H, s, C*H*$_3$C=O), 1.14 [3H, d, *J* = 6.0 Hz, CH(OMe)(C*H*$_3$)]; ^{13}C NMR (CDCl$_3$, DEPT–135) δ 207.4 (C, *C*=O), 73.0 (CH, *C*HOMe), 56.1 (CH$_3$, O*C*H$_3$), 50.4 (CH$_2$, *C*H$_2$C=O), 30.9 (CH$_3$, *C*H$_3$C=O), 19.1 [CH$_3$, CH(OMe)(*C*H$_3$)]; LRMS (ESI-TOF) m/z 117.10 (M$^+$+1), calcd. for $C_6H_{12}O_2$ 116.0837.



63eb

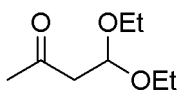
4-Ethoxy-pentan-2-one (63eb): Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν$_{max}$ 2976, 2930, 1717 (C=O), 1360 and 1103 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 3.82 (1H, sextet, *J* = 6.0 Hz, C*H*OEt), 3.50 (1H, p, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 3.34 (1H, br p, *J* = 7.2 Hz,

OC*H*$_2$CH$_3$), 2.66 (1H, dd, *J* = 15.6, 7.6 Hz, C*H*$_2$C=O), 2.36 (1H, dd, *J* = 15.6, 5.2 Hz, C*H*$_2$C=O), 2.17 (3H, s, C*H*$_3$C=O), 1.17 (3H, d, *J* = 6.8 Hz), 1.16 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$, DEPT–135) δ 207.5 (C, *C*=O), 71.4 (CH, *C*HOEt), 63.8 (CH$_2$, O*C*H$_2$CH$_3$), 50.6 (CH$_2$, *C*H$_2$C=O), 30.9 (CH$_3$, *C*H$_3$C=O), 19.8 (CH$_3$), 15.3 (CH$_3$, OCH*C*H$_3$); LRMS (ESI-TOF) m/z 131.10 (M$^+$+1), calcd. for $C_7H_{14}O_2$ 130.0994.



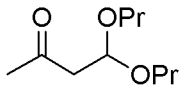
63fa

4,4-Dimethoxy-butan-2-one (63fa): Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν$_{max}$ 2936, 2835, 1713 (C=O), 1360 and 1120 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 4.79 [1H, t, *J* = 6.0 Hz, C*H*(OMe)$_2$], 3.36 (6H, s, 2 x OC*H*$_3$), 2.74 (2H, d, *J* = 5.6 Hz, C*H*$_2$C=O), 2.19 (3H, s, C*H*$_3$C=O); ^{13}C NMR (CDCl$_3$, DEPT–135) δ 205.3 (C, *C*=O), 101.3 [CH, C*H*(OMe)$_2$], 53.6 (2 x CH$_3$, 2 x O*C*H$_3$), 47.1 (CH$_2$, *C*H$_2$C=O), 30.9 (CH$_3$, *C*H$_3$C=O); LRMS (ESI-TOF) m/z 133 (M$^+$ +1), calcd. for $C_6H_{12}O_3$ 132.1577.



63fb'

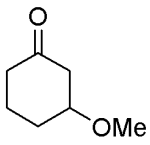
4,4-Diethoxy-butan-2-one (63fb'): Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν$_{max}$ 2964, 1717 (C=O), 1358, 1120 and 1070 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 4.84 [1H, t, *J* = 5.6 Hz, C*H*(OEt)$_2$], 3.61 (2H, br p, *J* = 7.2 Hz, OC*H*$_2$ CH$_3$), 3.47 (2H, br p, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 2.69 (2H, d, *J* = 5.6 Hz, C*H*$_2$C=O), 2.12 (3H, s, C*H*$_3$C=O), 1.13 (6H, t, *J* = 7.2 Hz, 2 x OCH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$, DEPT–135) δ 205.5 (C, *C*=O), 100.5 [CH, *C*H(OEt)$_2$], 62.3 (2 x CH$_2$, 2 x O*C*H$_2$CH$_3$), 47.6 (CH$_2$, *C*H$_2$C=O), 31.0 (CH$_3$, *C*H$_3$C=O), 15.1 (2 x CH$_3$, 2 x OCH$_2$*C*H$_3$).



63fc'

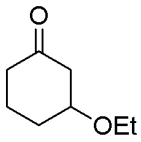
4,4-Dipropoxy-butan-2-one (63fc'): Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν$_{max}$ 2964, 1719 (C=O), 1464, 1358 and 1070 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 4.83 [1H, t, *J* = 6.0 Hz, C*H*(OPr)$_2$], 3.51 (2H, q, *J* = 6.8 Hz, OC*H*$_2$CH$_2$CH$_3$), 3.36 (2H, q, *J* = 6.8 Hz, OC*H*$_2$CH$_2$CH$_3$), 2.69 (2H, d, *J* = 5.6 Hz, C*H*$_2$C=O), 2.13 (3H, s, C*H*$_3$C=O), 1.55–1.50 (4H, m), 0.86 (6H, t, *J* = 7.6 Hz, 2 x C*H*$_3$); ^{13}C NMR (CDCl$_3$, DEPT–135) δ 205.8 (C, *C*=O), 99.9 [CH, *C*H(OPr)$_2$], 68.3 (2 x CH$_2$, 2 x O*C*H$_2$), 48.0

(CH_2, *C*H_2C=O), 31.1 (CH_3,*C*H_3C=O), 22.9 (2 x CH_2), 10.5 (2 x CH_3, 2 x $OCH_2CH_2CH_3$).



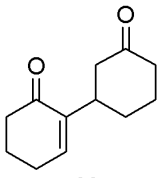
63ha

3-Methoxy-cyclohexanone (63ha): Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 2926, 2855, 1732 (C=O), 1462, 1379 and 1076 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.67 (1H, m, C*H*OMe), 3.32 (3H, s, OC*H*$_3$), 2.61 (1H, dd, *J* = 14.0, 4.0 Hz, C*H*$_2$C=O), 2.46 (1H, dd, *J* = 14.0, 6.8 Hz, C*H*$_2$C=O), 2.31 (2H, t, *J* = 6.4 Hz), 2.00–1.93 (2H, m), 1.82 (1H, m), 1.68 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 209.5 (C, *C*=O), 78.1 (CH, *C*HOMe), 55.9 (CH_3, OCH_3), 47.1 (CH_2, *C*H_2C=O), 41.1 (CH_2, *C*H_2C=O), 29.4 (CH_2), 20.5 (CH_2); LRMS (ESI-TOF) m/z 129.15 (M^++1), calcd. for $C_7H_{12}O_2$ 128.0837.

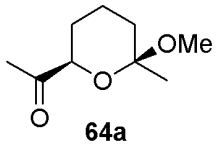


63hb

3-Ethoxy-cyclohexanone (63hb): Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 2926, 2855, 1732 (C=O), 1460, 1377 and 1080 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.73 (1H, m, C*H*OEt), 3.48 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 2.61 (1H, dd, *J* = 14.4, 4.0 Hz), 2.44 (1H, dd, *J* = 15.6, 4.8 Hz), 2.30 (2H, t, *J* = 6.8 Hz), 2.04–1.95 (2H, m), 1.81–1.18 (2H, m), 1.17 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 209.7 (C, *C*=O), 76.4 (CH, *C*HOEt), 63.6 (CH_2, O*C*H_2CH$_3$), 47.7 (CH_2, *C*H_2C=O), 41.1 (CH_2, *C*H_2C=O), 30.1 (CH_2), 20.7 (CH_2), 15.4 (CH_3, OCH_2CH_3); LRMS (ESI-TOF) m/z 165 (M+Na); calcd. for $C_8H_{14}O_2$ 142.0994.


69

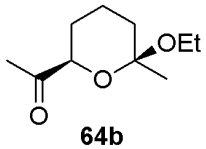
Bicyclohexyl-6-ene-2,3'-dione (69): Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 2938, 1711 (C=O), 1668 (C=O), 1389, 1344, 1317 and 1254 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.69 (1H, t, *J* = 4.0 Hz, olefinic-H), 2.98 (1H, br s), 2.40–2.30 (7H, m), 2.00–1.85 (4H, m), 1.74–1.55 (3H, m); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 211.2 (C, *C*=O), 198.4 (C, *C*=O), 144.3 (CH, olefinic-*C*H), 141.8 (C), 46.3 (CH_2), 41.2 (CH_2), 38.7 (CH_2), 37.6 (CH), 30.6 (CH_2), 26.0 (CH_2), 25.0 (CH_2),



64a

22.7 (CH_2); LRMS (ESI-TOF) m/z 193.10 (M^++1), calcd. for $C_{12}H_{16}O_2$ 192.1150.

1-(6-Methoxy-6-methyl-tetrahydro-pyran-2-yl)-ethanone (64a): Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 2951, 1720 (C=O), 1379, 1356, 1223, 1105 and 1041 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.98 (1H, dd, *J* = 12.0, 2.4 Hz), 3.20 (3H, s, OC*H*$_3$), 2.18 (3H, s, *C*H_3C=O), 1.87–1.80 (2H, m), 1.72 (1H, m), 1.64–1.58 (1H, m), 1.48–1.33 (1H, m), 1.33 (3H, s, CH_3), 1.28 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 209.4 (C, *C*=O), 98.4 (C), 76.0 (CH), 47.9 (CH_3, O*C*H_3), 34.9 (CH_2), 26.5 (CH_2), 25.7 (CH_3), 23.7 (CH_3, *C*H_3C=O), 18.3 (CH_2); LRMS (ESI-TOF) m/z 141.20 (M-OMe), calcd. for $C_9H_{16}O_3$ 172.1099.



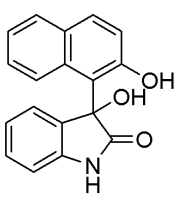
64b

1-(6-Ethoxy-6-methyl-tetrahydro-pyran-2-yl)-ethanone (64b): Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 2943, 1720 (C=O), 1356, 1222, 1062, 1041, 951 and 839 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.00 (1H, dd, *J* = 12.0, 2.8 Hz), 3.50–3.40 (2H, m, OC*H*$_2$*C*H_3), 2.18 (3H, s, C*H*$_3$), 1.93–1.82 (2H, m), 1.72 (1H, m), 1.63–1.55 (1H, m), 1.43 (1H, dt, *J* = 13.6, 4.4 Hz), 1.35 (3H, s, CH_3), 1.28 (1H, dd, *J* = 12.0, 4.0 Hz), 1.17 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 209.7 (C, *C*=O), 98.4 (C), 76.1 (CH), 55.5 (CH_2, O*C*H_2CH_3), 35.2 (CH_2), 26.7 (CH_2), 25.7 (CH_3), 24.5 (CH_3, *C*H_3C=O), 18.6 (CH_2), 15.4 (CH_3, OCH_2*C*H_3); LRMS (ESI-TOF) m/z 209.1 (M+Na), calcd. for $C_{10}H_{18}O_3$ 186.1256.

3. General experimental procedures for the Organo-Click reactions:

3a. Dimethylamino-ethanol-Catalyzed Friedel-Crafts Alkylation of 2-Naphthols with Substituted Isatins: In an ordinary glass vial equipped with a magnetic stirring bar, to 0.33 mmol of the 2-napthol **73** and 0.3 mmol of isatins **74a–l** was added 2.0 mL of CH_2Cl_2 solvent and then the catalyst dimethylamino-ethanol **2'c** (0.015 mmol) was added and the reaction mixture was stirred at 25 °C for the time indicated in Tables 8 and 9. Pure Friedel-Crafts alkylation products **75** were obtained by simple filtration of crude product through Wattmann filter paper with hexanes to produce 90–95% of

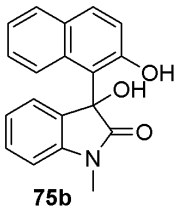
purity. High purity products were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).



75a

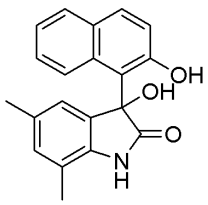
3-Hydroxy-3-(2-hydroxy-naphthalen-1-yl)-1,3-dihydro-indol-2-one (75a): Purified by filtration through Wattmann filter paper and isolated as a white solid. Mp 168–170 °C; IR (KBr): ν_{max} 3354, 3200, 3057, 1730 (O=C-NH), 1622, 1572, 1469, 1280, 1105, 1089, 960, 875 and 754 cm^{-1}; ^{1}H NMR [$CDCl_3$ + CD_3OD (five drops)] δ 8.35 (1H, m), 7.69 (1H, m), 7.46 (3H, m), 7.28 (1H, dt, *J* = 8.0, 1.2 Hz), 7.17 (1H, d, *J* = 8.4 Hz), 7.07 (1H, br d, *J* = 7.2 Hz), 6.92 (1H, d, *J* = 8.0 Hz), 6.71 (1H, d, *J* = 8.8 Hz); ^{13}C NMR [$CDCl_3$ + CD_3OD (five drops), DEPT–135] δ 179.9 (C, O=*C*-NH), 153.3 (C), 140.7 (C), 134.3 (C), 131.8 (C), 129.9 (CH), 126.9 (CH), 126.6 (CH), 125.9 (C), 125.5 (CH), 125.1 (CH), 123.9 (CH), 123.3 (CH), 122.4 (CH), 118.9 (CH), 115.8 (C), 110.4 (CH), 80.5 (C); HRMS m/z 314.0783 (M + Na^+), calcd. for $C_{18}H_{13}NO_3Na$ 314.0793; Anal. calcd. for $C_{18}H_{13}NO_3$ (291.0895): C, 74.22; H, 4.50; N, 4.81. Found: C, 74.283; H, 4.523; N, 4.765%.

3-Hydroxy-3-(2-hydroxy-naphthalen-1-yl)-1-methyl-1,3-dihydro-indol-2-one (75b):



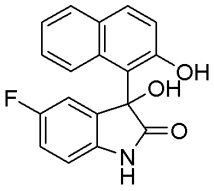
75b

Purified by column chromatography using EtOAc/hexane and isolated as a white solid. Mp 142–144 °C; IR (KBr): ν_{max} 3331, 3263, 2930, 1701 (O=C-NH), 1610, 1572, 1469, 1369, 1190, 1087, 981, 933, 804, 679, 567, 538, 493 and 464 cm^{-1}; ^{1}H NMR [$CDCl_3$ + CD_3OD (five drops)] δ 8.35 (1H, m), 7.68 (1H, m), 7.47 (3H, m), 7.37 (1H, t, *J* = 8.0 Hz), 7.16 (1H, d, *J* = 8.8 Hz), 7.13 (1H, t, *J* = 7.6 Hz), 6.92 (1H, d, *J* = 7.6 Hz), 6.66 (1H, d, *J* = 8.4 Hz), 3.24 (3H, s, NC*H*$_3$); ^{13}C NMR [$CDCl_3$ + CD_3OD (five drops), DEPT–135] δ 177.8 (C, O=*C*-NH), 153.3 (C), 142.9 (C), 134.3 (C), 131.2 (C), 130.0 (CH), 126.9 (CH), 126.6 (CH), 125.9 (C), 125.15 (CH), 125.10 (CH), 123.8 (CH), 123.7 (CH), 122.4 (CH), 118.9 (CH), 116.1 (C), 108.7 (CH), 80.0 (C), 26.3 (CH_3); Anal. calcd. for $C_{19}H_{15}NO_3$ (305.1052): C, 74.74; H, 4.95; N, 4.59. Found: C, 74.876; H, 4.910; N, 4.881%.



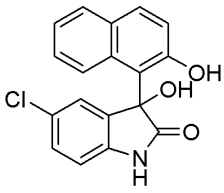
75c

3-Hydroxy-3-(2-hydroxy-naphthalen-1-yl)-5,7-dimethyl-1,3-dihydro-indol-2-one (75c): Purified by filtration through Wattmann filter paper and isolated as a white solid. Mp 128–130 °C; IR (KBr): ν_{max} 3271, 3047, 2918, 1712 (O=C-NH), 1624, 1574, 1394, 1209, 1143, 1086, 858, 752 and 570 cm^{-1}; ^{1}H NMR [$CDCl_3$ + CD_3OD (five drops)] δ 8.28 (1H, m), 7.62 (1H, m), 7.38 (2H, m), 7.10 (1H, d, *J* = 8.4 Hz), 7.00 (1H, s), 6.85 (1H, s), 6.66 (1H, d, *J* = 8.4 Hz), 2.19 (6H, s, 2 x CH_3); ^{13}C NMR [$CDCl_3$ + CD_3OD (five drops), DEPT–135] δ 180.2 (C, O=*C*-NH), 153.2 (C), 136.7 (C), 134.3 (C), 132.9 (C), 131.8 (CH), 131.7 (C), 127.0 (CH), 126.6 (CH), 125.9 (C), 125.0 (CH), 124.1 (CH), 123.3 (CH), 122.4 (CH), 119.6 (C), 118.9 (CH), 116.1 (C), 80.9 (C), 20.8 (CH_3), 15.9 (CH_3); Anal. calcd. for $C_{20}H_{17}NO_3$ (319.1208): C, 75.22; H, 5.37; N, 4.39. Found: C, 75.200; H, 5.353; N, 4.441%.



75d

5-Fluoro-3-hydroxy-3-(2-hydroxy-naphthalen-1-yl)-1,3-dihydro-indol-2-one (75d): Purified by filtration through Wattmann filter paper and isolated as a solid. Mp 158–160 °C; IR (KBr): ν_{max} 3339, 3063, 1739 (O=C-NH), 1699, 1631, 1572, 1489, 1386, 1190, 1093, 976, 746, 696, 578, 464 and 420 cm^{-1}; ^{1}H NMR (DMSO–D_6) δ 10.49 (1H, s, O=C-N*H*), 9.93 (1H, s, Ph-O*H*), 8.14 (1H, d, *J* = 8.8 Hz), 7.84 (1H, br d, *J* = 8.8 Hz), 7.54 (1H, d, *J* = 8.4 Hz), 7.45 (3H, m), 7.22 (1H, s, O-*H*), 7.07 (1H, dt, *J* = 9.2, 2.4 Hz), 6.90 (1H, dd, *J* = 8.4, 4.0 Hz), 6.84 (1H, dd, *J* = 7.6, 2.4 Hz); ^{13}C NMR (DMSO–D_6, DEPT–135) δ 179.0 (C, O=*C*-NH), 158.5 (C, d, *J* = 236.0 Hz), 150.7 (C), 139.4 (C), 135.3 (C, d, *J* = 7.0 Hz), 134.4 (C), 128.0 (CH), 126.6 (CH), 125.5 (CH), 125.3 (C), 125.1 (CH), 122.4 (CH), 121.4 (C), 119.2 (CH), 115.7 (CH, d, *J* = 23 Hz), 112.3 (CH, d, *J* = 24.0 Hz), 110.8 (CH, d, *J* = 8.0 Hz), 77.7 (C); HRMS m/z 332.0714 ($M + Na^+$), calcd. for $C_{18}H_{12}FNO_3Na$ 332.0699.

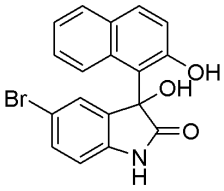


75e

5-Chloro-3-hydroxy-3-(2-hydroxy-naphthalen-1-yl)-1,3-dihydro-indol-2-one (75e): Purified by filtration through Wattmann filter paper and isolated as a white solid. Mp 140–142 °C; IR (KBr): ν_{max} 3290, 1705 (O=C-NH), 1618, 1575, 1473, 1394, 1120, 1028, 804, 713, 636, 551, 468 and 418 cm^{-1}; ^{1}H NMR [$CDCl_3$ + CD_3OD (five drops)] δ 8.27 (1H,

m), 7.65 (1H, m), 7.42 (2H, m), 7.33 (1H, m), 7.17 (2H, m), 6.89 (1H, d, *J* = 8.0 Hz), 6.67 (1H, d, *J* = 8.8 Hz); ^{13}C NMR [$CDCl_3$ + CD_3OD (five drops), DEPT–135] δ 179.5 (C, O=*C*-NH), 153.2 (C), 139.4 (C), 134.4 (C), 133.8 (C), 129.9 (CH), 128.5 (C), 127.1 (CH), 126.8 (CH), 125.9 (C), 125.7 (CH), 125.2 (CH), 123.6 (CH), 122.4 (CH), 119.2 (CH), 115.5 (C), 111.5 (CH), 80.4 (C); Anal. calcd. for $C_{18}H_{12}ClNO_3$ (325.0506): C, 66.37; H, 3.71; N, 4.30. Found: C, 66.336; H, 3.694; N, 4.413%.

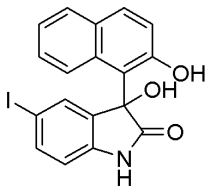
5-Bromo-3-hydroxy-3-(2-hydroxy-naphthalen-1-yl)-1,3-dihydro-indol-2-one (75f):



75f

Purified by filtration through Wattmann filter paper and isolated as a white solid. Mp 160–162 °C; IR (KBr): ν_{max} 3196, 1709 (O=C-NH), 1614, 1575, 1471, 1296, 1091, 989, 748, 696, 534 and 468 cm^{-1}; ^{1}H NMR [$CDCl_3$ + CD_3OD (five drops)] δ 8.33 (1H, m), 7.71 (1H, m), 7.53–7.36 (4H, m), 7.22 (1H, d, *J* = 8.4 Hz), 6.83 (1H, d, *J* = 8.0 Hz), 6.75 (1H, d, *J* = 8.8 Hz); ^{13}C NMR [$CDCl_3$ + CD_3OD (five drops), DEPT–135] δ 179.3 (C, O=*C*-NH), 153.1 (C), 139.9 (C), 134.2 (C), 134.1 (C), 132.6 (CH), 128.3 (CH), 126.9 (CH), 126.6 (CH), 125.7 (C), 125.1 (CH), 123.5 (CH), 122.2 (CH), 119.1 (CH), 115.6 (C), 115.4 (C), 111.9 (CH), 80.2 (C); HRMS m/z 391.9883 (M + Na^+), calcd. for $C_{18}H_{12}BrNO_3Na$ 391.9898; Anal. calcd. for $C_{18}H_{12}BrNO_3$ (369.0001): C, 58.40; H, 3.27; N, 3.78. Found: C, 58.409; H, 3.266; N, 3.856%.

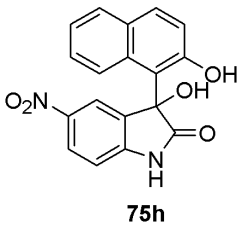
3-Hydroxy-3-(2-hydroxy-naphthalen-1-yl)-5-iodo-1,3-dihydro-indol-2-one (75g):



75g

Purified by filtration through Wattmann filter paper and isolated as a white solid. Mp 158–160 °C; IR (KBr): ν_{max} 3198, 2928, 1711 (O=C-NH), 1610, 1575, 1471, 1294, 1122, 1059, 877, 750, 630, 569 and 422 cm^{-1}; ^{1}H NMR [$CDCl_3$ + CD_3OD (five drops)] δ 8.29 (1H, m), 7.66 (2H, m), 7.54 (1H, dd, *J* = 8.4, 1.6 Hz), 7.43 (2H, m), 7.16 (1H, d, *J* = 8.4 Hz), 6.68 (1H, d, *J* = 8.4 Hz), 6.67 (1H, d, *J* = 8.0 Hz); ^{13}C NMR [$CDCl_3$ + CD_3OD (five drops), DEPT–135] δ 179.1 (C, O=*C*-NH), 153.2 (C), 140.6 (C), 138.7 (CH), 134.44 (C), 134.36 (C), 134.12 (CH), 127.1 (CH), 126.8 (CH), 125.9 (C), 125.3

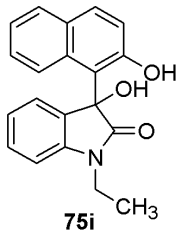
(CH), 123.6 (CH), 122.4 (CH), 119.2 (CH), 115.5 (C), 112.5 (CH), 85.6 (C), 80.2 (C); HRMS m/z 439.9771 ($M + Na^+$), calcd. for $C_{18}H_{12}INO_3Na$ 439.9760.



75h

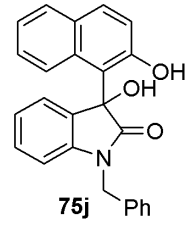
3-Hydroxy-3-(2-hydroxy-naphthalen-1-yl)-5-nitro-1,3-dihydro-indol-2-one (75h): Purified by filtration through Wattmann filter paper and isolated as a solid. Mp 156–158 °C; IR (KBr): ν_{max} 3312, 1732 (O=C-NH), 1624, 1604, 1521, 1473, 1340, 1224, 1180, 1084, 875, 833, 748, 634, 470 and 420 cm^{-1}; ^1H NMR (DMSO–D_6) δ 11.10 (1H, s, O=C-N*H*), 9.75 (1H, s, Ph-O*H*), 8.20 (1H, dd, *J* = 8.8, 2.4 Hz), 8.07 (1H, d, *J* = 8.0 Hz), 7.87 (2H, m), 7.64 (1H, d, *J* = 2.0 Hz), 7.54 (1H, d, *J* = 8.8 Hz), 7.43 (2H, m), 7.11 (1H, s, O-H), 7.09 (1H, d, *J* = 8.8 Hz); ^{13}C NMR (DMSO–D_6, DEPT–135) δ 179.3 (C, O=*C*-NH), 150.0 (C), 149.5 (C), 142.4 (C), 134.9 (C), 134.5 (C), 128.2 (CH), 126.7 (CH), 126.5 (CH), 125.4 (CH), 125.0 (C), 124.9 (CH), 122.5 (C), 122.3 (CH), 119.54 (CH), 119.52 (CH), 110.0 (CH), 75.7 (C); HRMS m/z 359.0659 ($M+Na^+$), calcd. for $C_{18}H_{12}N_2O_5Na$ 359.0644.

1-Ethyl-3-hydroxy-3-(2-hydroxy-naphthalen-1-yl)-1,3-dihydro-indol-2-one (75i):



75i

Purified by column chromatography using EtOAc/hexane and isolated as a white solid. Mp 160–162 ^oC; IR (KBr): ν_{max} 3344, 3310, 2974, 1703 (O=C-NH), 1610, 1385, 1097, 877, 756, 567, 493 and 466 cm^{-1}; ^1H NMR [$CDCl_3$ + CD_3OD (five drops)] δ 8.41 (1H, m), 7.55 (1H, br d, *J* = 7.2 Hz), 7.55 (1H, d, *J* = 7.2 Hz), 7.49 (2H, m), 7.39 (1H, t, *J* = 7.2 Hz), 7.21 (1H, d, *J* = 8.8 Hz), 7.15 (1H, t, *J* = 7.6 Hz), 6.96 (1H, d, *J* = 8.4 Hz), 6.74 (1H, d, *J* = 8.8 Hz), 3.80 (2H, m, NC*H*$_2$CH$_3$), 1.33 (3H, t, *J* = 7.2 Hz, NCH$_2$C*H*$_3$); ^{13}C NMR [$CDCl_3$ + CD_3OD (five drops), DEPT–135] δ 177.4 (C, O=*C*-NH), 153.3 (C), 141.9 (C), 134.3 (C), 131.4 (C), 129.9 (CH), 126.9 (CH), 126.6 (CH), 125.97 (C), 125.4 (CH), 125.1 (CH), 123.7 (CH), 123.5 (CH), 122.4 (CH), 119.0 (CH), 116.3 (C), 108.8 (CH), 80.0 (C), 34.9 (N*C*H$_2$CH$_3$), 12.2 (NCH$_2$*C*H$_3$); HRMS m/z 342.1112 ($M + Na^+$), calcd. for $C_{20}H_{17}NO_3Na$ 342.1106; Anal. calcd.

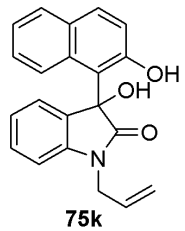


75j

for $C_{20}H_{17}NO_3$ (319.1208): C, 75.22; H, 5.37; N, 4.39. Found: C, 75.133; H, 5.379; N, 4.373%.

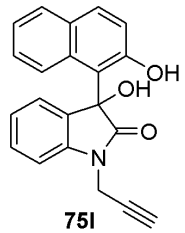
1-Benzyl-3-hydroxy-3-(2-hydroxy-naphthalen-1-yl)-1,3-dihydro-indol-2-one (75j): Purified by column chromatography using EtOAc/hexane and isolated as a white solid. Mp 100–102 °C; IR (KBr): ν_{max} 3254, 2922, 1705 (O=C-NH), 1612, 1572, 1469, 1174, 968, 802 and 752 cm^{-1}; ^1H NMR [$CDCl_3$ + CD_3OD (five drops)] δ 8.44 (1H, br d, *J* = 5.6 Hz), 7.50 (1H, m), 7.59–7.50 (3H, m), 7.33–7.17 (8H, m), 6.83 (2H, m), 5.02 (1H, d, *J* = 16.0 Hz), 4.86 (1H, d, *J* = 15.6 Hz); ^{13}C NMR [$CDCl_3$ + CD_3OD (five drops), DEPT–135] δ 177.97 (C, O=*C*-NH), 153.5 (C), 142.2 (C), 135.2 (C), 134.4 (C), 131.3 (C), 130.0 (CH), 128.8 (2 x CH), 127.8 (CH), 127.3 (2 x CH), 127.1 (CH), 126.8 (CH), 126.1 (C), 125.4 (CH), 125.3 (CH), 123.9 (CH), 123.8 (CH), 122.6 (CH), 119.2 (CH), 116.3 (C), 109.8 (CH), 80.2 (C), 44.0 (CH_2); HRMS m/z 404.1261 (M+Na), calcd. for $C_{25}H_{19}NO_3Na$ 404.1363; Anal. calcd. for $C_{25}H_{19}NO_3$ (381.1365): C, 78.72; H, 5.02; N, 3.67. Found: C, 78.675; H, 5.062; N, 3.772%.

1-Allyl-3-hydroxy-3-(2-hydroxy-naphthalen-1-yl)-1,3-dihydro-indol-2-one (75k):



75k

Purified by column chromatography using EtOAc/hexane and isolated as a white solid. Mp 150–152 °C; IR (KBr): ν_{max} 3342, 3288, 1703 (O=C-NH), 1610, 1572, 1383, 1288, 1176, 1080, 933, 800, 677, 495, 466 and 420 cm^{-1}; ^1H NMR [$CDCl_3$ + CD_3OD (five drops)] δ 8.32 (1H, m), 7.64 (1H, m), 7.43 (3H, m), 7.30 (1H, t, *J* = 7.6 Hz), 7.14 (1H, d, *J* = 8.4 Hz), 7.08 (1H, t, *J* = 7.2 Hz), 6.88 (1H, d, *J* = 8.0 Hz), 6.63 (1H, d, *J* = 8.4 Hz), 5.83 (1H, m, C*H*=CH_2), 5.26 (1H, d, *J* = 19.0 Hz), 5.22 (1H, d, *J* = 11.2 Hz) [CH=CH_2]; 4.33 (2H, dABq, *J* = 16.4, 5.2 Hz, NCH_2CH=CH_2); ^{13}C NMR [$CDCl_3$ + CD_3OD (five drops), DEPT–135] δ 177.6 (C, O=*C*-NH), 153.4 (C), 142.2 (C), 134.4 (C), 131.3 (C), 130.7 (CH), 129.9 (CH), 127.1 (CH), 126.7 (CH), 126.0 (C), 125.3 (CH), 125.2 (CH), 123.8 (CH), 123.7 (CH), 122.5 (CH), 119.1 (CH), 117.9 (CH_2,



75l

CH=*C*H_2), 116.3 (C), 109.7 (CH), 80.0 (C), 42.5 (CH_2, N*C*H_2CH=CH_2); HRMS m/z 354.1101 ($M+Na^+$), calcd. for $C_{21}H_{17}NO_3Na$ 354.1106.

3-Hydroxy-3-(2-hydroxy-naphthalen-1-yl)-1-prop-2-ynyl-1,3-dihydro-indol-2-one (75l): Purified by column chromatography using EtOAc/hexane and isolated as a white solid. Mp 154–156 °C; IR (KBr): ν_{max} 3368, 3292, 2127, 1701 (O=C-NH), 1614, 1572, 1467, 1286, 1054, 758, 640, 561 and 466 cm^{-1}; ^{1}H NMR [$CDCl_3$ + CD_3OD (five drops)] δ 8.36 (1H, br d, *J* = 6.8 Hz), 7.69 (1H, m), 7.53 (1H, d, *J* = 7.2 Hz), 7.47 (2H, m), 7.41 (1H, t, *J* = 8.0 Hz), 7.19–7.13 (3H, m), 6.66 (1H, d, *J* = 8.4 Hz), 4.53 (2H, d, *J* = 2.0 Hz, NC*H*$_2$C≡CH), 2.31 (1H, t, *J* = 2.0 Hz, NCH$_2$C≡C*H*); ^{13}C NMR [$CDCl_3$ + CD_3OD (five drops), DEPT–135] δ 176.7 (C, O=*C*-NH), 153.1 (C), 141.0 (C), 134.2 (C), 131.3 (C), 129.8 (CH), 126.9 (CH), 126.5 (CH), 125.7 (C), 125.08 (CH), 125.02 (CH), 123.9 (CH), 123.6 (CH), 122.2 (CH), 118.9 (CH), 115.7 (C), 109.5 (CH), 79.8 (C), 76.2 (C, NCH$_2$*C*≡CH), 72.6 (CH, NCH$_2$C≡*C*H), 29.3 (CH_2, N*C*H$_2$C≡CH); Anal. calcd. for $C_{21}H_{15}NO_3$ (329.1052): C, 76.58; H, 4.59; N, 4.25. Found: C, 76.540; H, 4.561; N, 4.221%.

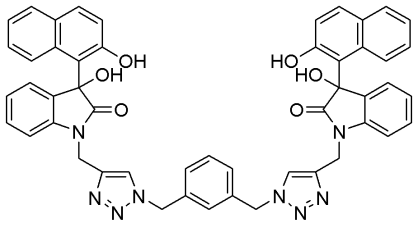
3b. Dimethylamino-ethanol/Cu^I-Catalyzed Friedel-Crafts Alkylation/Huisgen Cycloaddition Reactions in One-Pot: In an ordinary glass vial equipped with a magnetic stirring bar, to 0.33 mmol of the 2-napthol **73** and 0.3 mmol of isatin **74l** was added 2.0 mL of CH_2Cl_2 solvent and then the catalyst dimethylamino-ethanol **2'c** (0.015 mmol) was added and the reaction mixture was stirred at 25 °C for the time indicated in Table 10. Solvent CH_2Cl_2 was removed by vacuum pump, then EtOH (2.0 mL), $CuSO_4$ (0.33 mmol), Cu wire (5 mg) and benzyl azide **21a** (0.33 mmol) or bis-azidomethyl-benzenes **21b-d** (0.165 mmol) were added and stirring continued at the same temperature for the time indicated in Table 10. The crude reaction mixture was directly loaded on silica gel column without aqueous work-up and pure cascade products **76** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

1-(1-Benzyl-1H-[1,2,3]triazol-4-ylmethyl)-3-hydroxy-3-(2-hydroxy-naphthalen-1-yl)-1,3-dihydro-indol-2-one (76la): Purified by column chromatography using EtOAc/hexane and isolated as a white solid. Mp 172–174 °C; IR (KBr): ν_{max} 3350, 3130, 2928, 1695 (O=C-NH), 1608, 1485, 1369, 1228, 1168, 1064, 815, 736, 569, 491 and 426 cm^{-1}; ^1H NMR (DMSO–D_6) δ 8.12 (1H, br d, *J* = 8.0 Hz), 8.11 (1H, s, olefin-*H*), 7.83 (1H, br d, *J* = 8.0 Hz), 7.46 (3H, m), 7.43–7.25 (7H, m), 7.12 (1H, d, *J* = 8.0 Hz), 7.06 (1H, d, *J* = 7.6 Hz), 6.96 (1H, t, *J* = 7.6 Hz), 5.60 (2H, s), 5.03 (2H, s); ^{13}C NMR (DMSO–D_6, DEPT–135) δ 176.7 (C, O=*C*-NH), 150.5 (C), 143.3 (C), 142.9 (C), 136.5 (C), 134.3 (C), 132.9 (C), 129.6 (CH), 129.3 (2 x CH), 128.6 (CH), 128.4 (2 x CH), 127.9 (CH), 126.6 (CH), 125.4 (C), 125.3 (CH), 124.99 (CH), 124.5 (CH), 124.1 (CH), 122.9 (CH), 122.4 (CH), 121.6 (C), 119.3 (CH), 109.6 (CH), 77.2 (C), 53.4 (CH_2), 35.6 (CH_2); HRMS m/z 485.1573 (M+Na), calcd. for $C_{28}H_{22}N_4O_3Na$ 485.1590.

76la

1,2-Bis-[3-Hydroxy-3-(2-hydroxy-naphthalen-1-yl)-1-(1-methylen-1-yl-1H-[1,2,3]triazol-4-ylmethyl)-1,3-dihydro-indol-2-one]-benzene (76lb): Purified by column chromatography using EtOAc/hexane and isolated as a white solid. Mp 120-122 °C; IR (KBr): ν_{max} 3252, 2926, 1716 (O=C-NH), 1612, 1574, 1467, 1172, 1047, 877, 750, 569, 482 and 420 cm^{-1}; ^1H NMR (DMSO–D_6) δ 8.22 (2H, br d, *J* = 6.8 Hz), 8.21 (2H, br s, olefin-*H*), 7.94 (2H, d, *J* = 7.6 Hz), 7.61–7.50 (8H, m), 7.44 (2H, m), 7.39 (2H, t, *J* = 7.6 Hz), 7.23 (4H, m), 7.17(2H, d, *J* = 7.6 Hz), 7.07 (2H, t, *J* = 7.6 Hz), 5.93 (4H, s), 5.14 (4H, s); ^{13}C NMR (DMSO–D_6, DEPT–135) δ 176.8 (2 x C, O=*C*-NH), 150.4 (2 x C), 143.3 (2 x C), 142.97 (2 x C), 134.6 (2 x C), 134.3 (2 x C), 132.9 (2 x C), 129.6 (2 x CH), 129.5 (2 x CH), 129.3 (2 x CH), 127.97 (2 x CH), 126.6 (2 x CH), 125.44 (2 x CH), 125.38 (2 x C), 125.0 (2 x CH), 124.5 (2 x CH), 124.4 (2 x CH), 122.99 (2 x CH), 122.4 (2 x CH), 121.7 (2 x C), 119.3 (2 x CH), 109.6 (2 x CH),

76lb

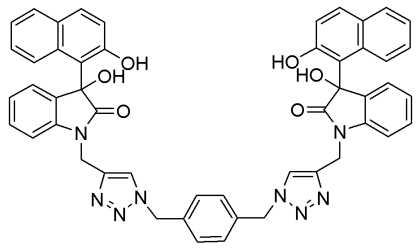


76lc

77.2 (2 x C), 50.5 (2 x CH_2), 35.6 (2 x CH_2); Anal. calcd. for $C_{50}H_{36}N_8O_6$ (846.2914): C, 70.91; H, 4.52; N, 13.23. Found: C, 71.072; H, 4.342; N, 13.172%.

1,3-Bis-[3-Hydroxy-3-(2-hydroxy-naphthalen-1-yl)-1-(1-methylen-1-yl-1H-[1,2,3]triazol-4-ylmethyl)-1,3-dihydro-indol-2-one]-benzene (76lc): Purified by column chromatography using EtOAc/hexane and isolated as a solid. Mp 138–140 °C; IR (KBr): ν_{max} 3260, 3140, 3053, 2926, 1718 (O=C-NH), 1612, 1574, 1433, 1363, 1172, 1091, 877, 750, 570, 478 and 422 cm^{-1}; ^1H NMR (DMSO–D_6) δ 8.15 (2H, br d, *J* = 8.0 Hz), 8.10 (2H, br s, olefin-*H*), 7.82 (2H, br d, *J* = 8.0 Hz), 7.49–7.22 (16H, m), 7.10 (2H, d, *J* = 8.0 Hz), 7.05 (2H, d, *J* = 7.2 Hz), 6.95 (2H, t, *J* = 7.6 Hz), 5.58 (4H, s), 5.02 (4H, s); ^{13}C NMR (DMSO–D_6, DEPT–135) δ 176.8 (2 x C, O=*C*-NH), 150.5 (2 x C), 143.3 (2 x C), 142.9 (2 x C), 137.0 (2 x C), 134.3 (2 x C), 132.9 (2 x C), 129.8 (CH), 129.6 (2 x CH), 128.2 (2 x CH), 128.05 (CH), 128.00 (2 x CH), 126.6 (2 x CH), 125.5 (2 x CH), 125.4 (2 x C), 125.0 (2 x CH), 124.5 (2 x CH), 124.2 (2 x CH), 123.0 (2 x CH), 122.4 (2 x CH), 121.7 (2 x C), 119.3 (2 x CH), 109.6 (2 x CH), 77.2 (2 x C), 53.1 (2 x CH_2), 35.6 (2 x CH_2); Anal. calcd. for $C_{50}H_{36}N_8O_6$ (846.2914): C, 70.91; H, 4.52; N, 13.23. Found: C, 70.811; H, 4.582; N, 13.299%.

1,4-Bis-[3-Hydroxy-3-(2-hydroxy-naphthalen-1-yl)-1-(1-methylen-1-yl-1H-[1,2,3]triazol-4-ylmethyl)-1,3-dihydro-indol-2-one]-benzene (76ld): Purified by column chromatography using EtOAc/hexane and isolated as a white solid. Mp 130–132 °C; IR (KBr): ν_{max} 3271, 2926, 1726 (O=C-NH), 1612, 1574, 1467, 1292, 1091, 968, 806, 750, 570, 478 and 424 cm^{-1}; ^1H NMR (DMSO–D_6) δ 8.10 (2H, br d, *J* = 8.0 Hz), 8.09 (2H, br s, olefin-*H*), 7.82 (2H, d, *J* = 7.6 Hz), 7.49–7.39 (8H, m), 7.30 (3H, br s), 7.25 (3H, t, *J* = 8.0 Hz), 7.09–7.03 (4H, m), 6.94 (2H, t, *J* = 7.6 Hz), 5.58 (4H, s), 4.99 (4H, s); ^{13}C NMR (DMSO–D_6, DEPT–135) δ 176.8 (2 x C, O=*C*-NH), 150.4 (2 x C), 143.3 (2 x C), 142.9 (2 x C), 136.4 (2 x C), 134.3 (2 x C), 132.9 (2 x C), 129.6 (2 x CH), 128.8 (4 x CH), 127.99 (2 x CH), 126.6 (2



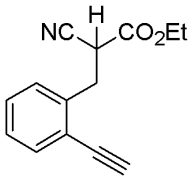
76ld

x CH), 125.45 (2 x CH), 125.38 (2 x C), 125.0 (2 x CH), 124.5 (2 x CH), 124.1 (2 x CH), 123.0 (2 x CH), 122.4 (2 x CH), 121.7 (2 x C), 119.3 (2 x CH), 109.6 (2 x CH), 77.2 (2 x C), 53.0 (2 x CH_2), 35.6 (2 x CH_2); Anal. calcd. for $C_{50}H_{36}N_8O_6$ (846.2914): C, 70.91; H, 4.52; N, 13.23. Found: C, 71.019; H, 4.544; N, 13.388%.

4. General experimental procedures for the multi-catalysis cascade reactions:

4a. Amino Acid-Catalyzed Three-component Cascade O/H Reactions: In an ordinary glass vial equipped with a magnetic stirring bar, to 0.5 mmol of 2-ethynyl-benzaldehyde **5d**, 0.5 mmol of CH-acid **20** and 0.5 mmol of Hantzsch ester **77a,** was added 2.0 mL of solvent and then the catalyst L-proline (0.1 mmol, 20 mol-%, 11.5 mg) was added and the reaction mixture was stirred at 25 °C for 0.5 to 24 h. The crude reaction mixture was directly loaded onto a silica gel column with or without aqueous work-up and pure one-pot products **79** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

4b. Amino Acid-Catalyzed Four-component Cascade O/H Reactions: In an ordinary glass vial equipped with a magnetic stirring bar, to 0.5 mmol of 2-ethynyl-benzaldehyde **5d** and 0.5 mmol of CH-acid **20,** was added 2.0 mL of solvent and then the catalyst L-proline (0.1 mmol, 20 mol-%, 11.5 mg) was added and the reaction mixture was stirred at 25 °C for 1.5 to 4 h, then o-phenylenediamine **82** (0.5 mmol) and benzaldehyde (0.5 mmol) were added and stirred for 12 h. Pure one-pot products **79** were obtained by simple filtration of crude product through sintered funnel with dichloromethane in 85–90% purity. High purity products were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

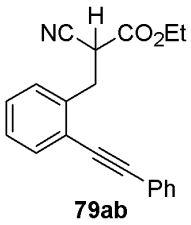


79db

2-Cyano-3-(2-ethynyl-phenyl)-propionic acid ethyl ester (79db): Purified by column chromatography using EtOAc/hexane and isolated as a liquid. IR (Neat): ν_{max} 3289, 2986, 1745 (O-C=O), 1447, 1370,

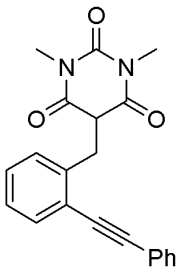
1263, 1206, 1162, 1029 and 762 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.52 (1H, d, *J* = 7.2 Hz, Ar-*H*), 7.35–7.25 (3H, m, Ar-*H*), 4.25 (1H, q, *J* = 7.6 Hz, $CO_2CH_2CH_3$), 4.24 (1H, q, *J* = 7.6 Hz, $CO_2CH_2CH_3$), 3.98 (1H, dd, *J* = 9.2, 6.4 Hz, $ArCH_2CH$), 3.56 (1H, dd, *J* = 13.6, 6.4 Hz, $ArCH_2CH$), 3.37 (1H, s, Ar-C≡C*H*), 3.26 (1H, dd, *J* = 13.6, 9.2 Hz, $ArCH_2CH$), 1.28 (3H, t, *J* = 7.2 Hz, $CO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 165.5 (C, O-C=O), 137.8 (C), 133.2 (CH), 130.0 (CH), 129.3 (CH), 127.8 (CH), 121.7 (C), 116.1 (C, CN), 82.6 (CH, Ar-C≡*CH*), 81.0 (C, Ar-*C*≡CH), 62.9 (CH_2, $CO_2CH_2CH_3$), 37.9 (CH), 34.6 (CH_2), 13.9 (CH_3, $CO_2CH_2CH_3$). LRMS m/z 227.85 (M^+), calcd. for $C_{14}H_{13}NO_2$ 227.0946; Anal. calcd. for $C_{14}H_{13}NO_2$ (227.0946): C, 73.99; H, 5.77; N, 6.16; Found: C, 73.92; H, 5.74; N, 6.20%.

2-Cyano-3-(2-phenylethynyl-phenyl)-propionic acid ethyl ester (79ab): Purified by column chromatography using EtOAc/hexane and isolated as a liquid; IR (neat): ν_{max} 1745 (O-C=O), 1495, 1446, 1370, 1262, 1199, 1162, 1096, 1029, 759, 691 and 636 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.60–7.50 (3H, m, Ar-*H*), 7.40–7.32 (4H, m, Ar-*H*), 7.32–7.27 (2H, m, Ar-*H*), 4.24 (2H, m, $CO_2CH_2CH_3$), 4.06 (1H, dd, *J* = 9.6, 6.0 Hz), 3.66 (1H, dd, *J* = 13.6, 6.0 Hz), 3.26 (1H, dd, *J* = 13.6, 9.6 Hz), 1.25 (3H, t, *J* = 7.2 Hz, $CO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 165.6 (C, O-*C*=O), 137.0 (C), 132.4 (CH), 131.5 (2 x CH), 130.0 (CH), 128.9 (CH), 128.7 (CH), 128.4 (2 x CH), 127.8 (CH), 122.7 (C), 122.5 (C), 116.1 (C, *C*N), 94.8 (C), 86.4 (C), 62.8 (CH_2, $CO_2CH_2CH_3$), 38.2 (CH), 35.1 (CH_2), 13.8 (CH_3, $CO_2CH_2CH_3$). LRMS m/z 303.95 (M^+), calcd. for $C_{20}H_{17}NO_2$ 303.1259; Anal. calcd. for $C_{20}H_{17}NO_2$ (303.1259): C, 79.19; H, 5.65; N, 4.62. Found C, 79.24; H, 5.61; N, 4.68%.



79ab

1,3-Dimethyl-5-(2-phenylethynyl-benzyl)-pyrimidine-2,4,6-trione (79aa): Purified by column chromatography using EtOAc/hexane and isolated as a solid. IR (neat): ν_{max} 1686, 1672, 1446, 1373, 1281, 1112 and 756 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.62 (2H, dd, *J* = 8.0 and 2.0 Hz,



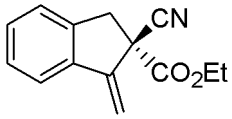
79aa

Ar-*H*), 7.52–7.50 (1H, m, Ar-*H*), 7.38–7.35 (3H, m, Ar-*H*), 7.25 (2H, dd, *J* = 6.0, 3.6 Hz, Ar-*H*), 7.13 (1H, m, Ar-*H*), 3.94 (1H, t, *J* = 6.0 Hz), 3.65 (2H, d, *J* = 6.0 Hz), 3.14 (6H, s, 2 x NCH_3); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 168.1 (2 x C, 2 x N-*C*=O), 151.4 (C), 137.0 (C), 132.6 (CH), 131.6 (2 x CH), 129.9 (CH), 128.5 (CH), 128.4 (2 x CH), 128.2 (CH), 127.6 (CH), 123.2 (C), 122.8 (C), 93.9 (C), 86.8 (C), 50.7 (CH), 36.6 (CH_2), 28.4 (2 x CH_3, 2 x N*C*H_3). LRMS m/z 347.05 (M^+ +1), calcd. for $C_{21}H_{18}N_2O_3$ 346.1317; Anal. calcd. for $C_{21}H_{18}N_2O_3$ (346.1317): C, 72.82; H, 5.24; N, 8.09. Found C, 72.75; H, 5.28; N, 8.13%.

4d. Amino Acid-/CuI-/Base-Catalyzed CC Reactions: In an ordinary glass vial equipped with a magnetic stirring bar, to 0.5 mmol of functionalized acetylenes **79,** was added 3.3 mL of solvent and then the catalyst amino acid, L-proline (0.075 mmol, 15 mol-%, 8.6 mg), CuI (0.05 mmol, 10 mol-%, 9.5 mg) and Cs_2CO_3 (1.0 mmol, 2 equiv., 326 mg) were added and the reaction mixture was stirred at 25 °C for the time indicated in Table A1. 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 CC products **80** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

4e. Amino Acid-/CuI-/Base-Catalyzed Cascade O/H/CC Reactions in One-Pot: In an ordinary glass vial equipped with a magnetic stirring bar, to 0.5 mmol of 2-ethynyl-benzaldehyde **5d**, 0.5 mmol of CH-acid **20** and 0.5 mmol of Hantzsch ester **77a,** was added 2.0 mL of solvent and then the catalyst L-proline (0.1 mmol, 20 mol-%, 11.5 mg) was added and the reaction mixture was stirred at 25 °C for 0.5 to 24 h as shown in Table 11. To the crude reaction mixture was added CuI (0.05 mmol, 10 mol-%, 9.5 mg), Cs_2CO_3 (1 mmol, 2 equiv., 326 mg) and CH_3CN (1.0 mL) and stirred at 25 °C for 0.5 to 2 h as shown in Table 11. 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.

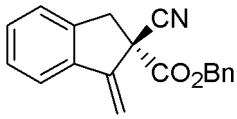
Pure cascade products **80** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).



80db

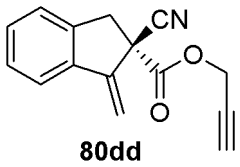
2-Cyano-1-methylene-indan-2-carboxylic acid ethyl ester (80db): Purified by column chromatography using EtOAc/hexane and isolated as a liquid. The enantiomeric excess (ee) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AS-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ□= 254 nm), t_R = 7.30 min (minor), t_R = 9.71 min (major). ≤5% ee; IR (neat): ν_{max} 2985, 1737 (O-C=O), 1644 (C=C), 1470, 1260, 1226, 1120, 1062, 1018, 908, 778 and 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.49 (1H, d, *J* = 6.8 Hz, Ar-*H*), 7.35–7.26 (3H, m, Ar-*H*), 5.82 (1H, s, olefinic-*H*), 5.65 (1H, s, olefinic-*H*), 4.33–4.24 (2H, m, $CO_2CH_2CH_3$), 3.87 (1H, d, *J* = 16.8 Hz), 3.58 (1H, d, *J* = 16.4 Hz), 1.31 (3H, t, *J* = 7.2 Hz, $CO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 167.1 (C, O-*C*=O), 147.1 (C), 141.3 (C), 136.6 (C), 130.1 (CH), 127.9 (CH), 125.0 (CH), 121.4 (CH), 119.4 (C, *C*N), 108.7 (CH_2), 63.4 (CH_2, $CO_2CH_2CH_3$), 50.5 (C), 41.1 (CH_2), 13.9 (CH_3, $CO_2CH_2CH_3$). LRMS m/z 227.85 (M^+), calcd. for $C_{14}H_{13}NO_2$ 227.0946; Anal. calcd. for $C_{14}H_{13}NO_2$ (227.0946): C, 73.99; H, 5.77; N, 6.16. Found C, 73.89; H, 5.73; N, 6.23%.

2-Cyano-1-methylene-indan-2-carboxylic acid benzyl ester (80dc): Purified by column chromatography using EtOAc/hexane and isolated as a liquid. IR (neat): ν_{max} 3033, 1747 (O-C=O), 1642 (C=C), 1459, 1251, 1196, 1056, 902, 776, 733 and 697 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.45 (1H, m, Ar-*H*), 7.37–7.26 (8H, m, Ar-*H*), 5.76 (1H, d, *J* = 1.2 Hz, olefinic-*H*), 5.58 (1H, d, *J* = 1.2 Hz, olefinic-*H*), 5.23 (2H, ABq, *J* = 12.4 Hz, CO_2CH_2Ph), 3.86 (1H, d, *J* = 16.4 Hz), 3.57 (1H, d, *J* = 16.8 Hz); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 166.8 (C, O-*C*=O), 146.8 (C), 141.1 (C), 136.5 (C), 134.5 (C), 130.1 (CH), 128.61 (2 x CH), 128.58 (CH), 128.0 (2 x CH), 127.8 (CH), 124.9 (CH), 121.4 (CH), 119.1 (C, *C*N), 108.9 (CH_2), 68.7 (CH_2, CO_2CH_2Ph), 50.5 (C), 41.0 (CH_2). LRMS m/z 289.00 (M^+),



80dc

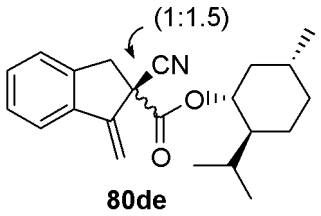
calcd. for $C_{19}H_{15}NO_2$ 289.1103; Anal. calcd. for $C_{19}H_{15}NO_2$ (289.1103): C, 78.87; H, 5.23; N, 4.84. Found C, 78.91; H, 5.27; N, 4.92%.



80dd

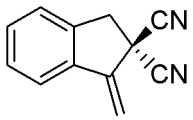
2-Cyano-1-methylene-indan-2-carboxylic acid prop-2-ynyl ester (80dd): Purified by column chromatography using EtOAc/hexane and isolated as a liquid. IR (neat): ν_{max} 3269, 1751 (O-C=O), 1247, 1200, 1058, 941, 898, 777, 724, 685 and 651 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.48 (1H, d, *J* = 6.8 Hz, Ar-*H*), 7.35–7.25 (3H, m, Ar-*H*), 5.83 (1H, d, *J* = 1.6 Hz, olefinic-*H*), 5.67 (1H, d, *J* = 1.6 Hz, olefinic-*H*), 4.79 (2H, dABq, *J* = 15.6, 2.4 Hz, $CO_2CH_2C{\equiv}CH$), 3.88 (1H, d, *J* = 16.4 Hz), 3.60 (1H, d, *J* = 16.8 Hz), 2.52 (1H, t, *J* = 2.4 Hz, $CO_2CH_2C{\equiv}CH$); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 166.3 (C, O-C=O), 146.5 (C), 140.9 (C), 136.4 (C), 130.1 (CH), 127.9 (CH), 124.9 (CH), 121.4 (CH), 118.8 (C, CN), 109.1 (CH_2), 76.1 (CH, C≡*C*H), 76.0 (C, *C*≡CH), 54.4 (CH_2, $CO_2CH_2C{\equiv}CH$), 50.2 (C), 41.0 (CH_2). LRMS m/z 237.60 (M^+), calcd. for $C_{15}H_{11}NO_2$ 237.0790; Anal. calcd. for $C_{15}H_{11}NO_2$ (237.0790): C, 75.94; H, 4.67; N, 5.90; Found C, 75.85; H, 4.71; N, 6.02%.

2-Cyano-1-methylene-indan-2-carboxylic acid 2-isopropyl-5-methyl-cyclohexyl ester (80de): Purified by column chromatography using EtOAc/hexane and isolated as a gummy liquid. **$[\alpha]_D^{25}$ = –63.3°** (*c* = 0.5 g/100 mL, $CHCl_3$, **20% *de***); IR (neat): ν_{max} 2957, 2929, 2870, 1738 (O-C=O), 1643 (C=C), 1461, 1250, 1218, 1055, 950, 908, 776 and 732 cm^{-1}; ^1H NMR ($CDCl_3$, 1:1.5 mixture of two diastereomers) δ 7.49 (2H, m, Ar-*H*), 7.35–7.26 (6H, m, Ar-*H*), 5.82 (2H, s, 2 x olefinic-*H*), 5.65 (1H, s, olefinic-*H*), 5.62 (1H, s, olefinic-*H*), 4.70 (2H, dt, *J* = 12.0, 4.0 Hz), 3.84 (2H, t, *J* = 16.0 Hz), 3.58 (2H, dd, *J* = 16.0, 4.0 Hz), 1.99 (2H, m), 1.90–1.75 (2H, m), 1.70 (4H, m), 1.45 (4H, m), 1.15–1.00 (4H, m), 1.00–0.85 (14H, m), 0.73 (3H, d, *J* = 8.0 Hz), 0.71 (3H, d, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT–135, 1:1.5 mixture of two diastereomers) δ 166.7 (C, O-C=O), 166.5 (C, O-C=O), 147.22 (C), 147.20 (C), 141.44 (C), 141.23 (C), 136.77 (C), 136.59 (C), 129.99 (CH), 129.96 (CH), 127.77



80de

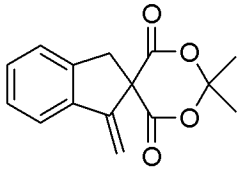
(CH), 127.71 (CH), 124.92 (CH), 124.89 (CH), 121.31 (2 x CH), 119.38 (C, CN), 119.31 (C, CN), 108.4 (2 x CH_2), 77.79 (CH), 77.70 (CH), 51.02 (C), 50.67 (C), 46.80 (CH), 46.73 (CH), 41.3 (CH_2), 40.89 (CH_2), 40.00 (CH_2), 39.97 (CH_2), 34.07 (CH_2), 33.99 (CH_2), 31.37 (2 x CH), 26.04 (2 x CH), 23.26 (CH_2), 23.03 (CH_2), 21.93 (2 x CH_3), 20.80 (CH_3), 20.70 (CH_3), 16.11 (CH_3), 15.89 (CH_3); LRMS m/z 338.00 (M^+ + 1), calcd. for $C_{22}H_{27}NO_2$ 337.2042; Anal. calcd. for $C_{22}H_{27}NO_2$ (337.2042): C, 78.30; H, 8.06; N, 4.15. Found C, 78.25; H, 8.11; N, 4.19%.



80df

1-Methylene-indan-2,2-dicarbonitrile (80df): Purified by column chromatography using EtOAc/hexane and isolated as a liquid. IR (neat): ν_{max} 3623, 3596, 3383, 2252, 1648 (C=C), 1470, 1439, 1074, 906, 776, 732, 701, 686, 678 and 652 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.56 (1H, d, *J* = 6.4 Hz, Ar-*H*), 7.42–7.36 (2H, m, Ar-*H*), 7.32 (1H, d, *J* = 7.2 Hz, Ar-*H*), 5.93 (1H, d, *J* = 2.4 Hz, olefinic-*H*), 5.80 (1H, d, *J* = 2.4 Hz, olefinic-*H*), 3.81 (2H, s); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 144.1 (C), 138.3 (C), 135.3 (C), 130.8 (CH), 128.8 (CH), 125.2 (CH), 121.9 (CH), 115.4 (2 x C, 2 x CN), 110.7 (CH_2), 43.3 (CH_2), 37.4 (C). LRMS m/z 178.70 (M^+-1), calcd. for $C_{12}H_8N_2$ 180.0687; Anal. calcd. for $C_{12}H_8N_2$ (180.0687): C, 79.98; H, 4.47; N, 15.55. Found C, 79.85; H, 4.49; N, 15.62%.

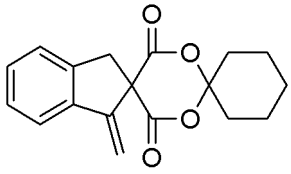
2,2-Dimethyl-1'-methylenespiro[dihydro-4*H*-[1,3]dioxane-5,2'-(2',3'-dihydro-1'*H*-indene)]-4,6-dione (80dg): Purified by column chromatography using EtOAc/hexane and isolated as a solid. IR (neat): ν_{max} 1743 (O-C=O), 1388, 1282, 1252, 1199, 1097, 1066, 1026, 948, 853, 778 and 728 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.49 (1H, d, *J* = 7.6 Hz, Ar-*H*), 7.33–7.26 (3H, m, Ar-*H*), 5.72 (1H, d, *J* = 2.0 Hz, olefinic-*H*), 5.26 (1H, d, *J* = 2.0 Hz, olefinic-*H*), 3.71 (2H, s), 1.86 (3H, s, CH_3), 1.75 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 169.2 (2 x C, 2 x O-C=O), 152.2 (C), 142.8 (C), 136.9 (C), 130.1 (CH), 127.6 (CH), 125.0 (CH), 121.4 (CH), 106.2 (CH_2), 105.2 (C, O-C-O), 57.9 (C), 40.2 (CH_2), 30.5 (CH_3), 27.6 (CH_3). LRMS m/z 258.95 (M^+), calcd. for $C_{15}H_{14}O_4$



80dg

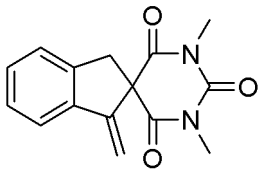
258.0892; Anal. calcd. for $C_{15}H_{14}O_4$ (258.0892): C, 69.76; H, 5.46; Found C, 69.65; H, 5.50%.

1’’-Methylenedispiro[cyclohexane-1,2’-(dihydro-4’*H*-[1,3]dioxane)-5’,2’’-(2’’,3’’-dihydro-1’’*H*-indene)]-4’,6’-dione (80dh): Purified by column chromatography using EtOAc/hexane and isolated as a solid. IR (neat): ν_{max} 2948, 2902, 1745 (O-C=O), 1396, 1369, 1289, 1264, 1238, 1133, 1079, 961, 776 and 732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.49 (1H, d, *J* = 7.6 Hz, Ar-*H*), 7.35–7.26 (3H, m, Ar-*H*), 5.72 (1H, d, *J* = 2.0 Hz, olefinic-*H*), 5.28 (1H, d, *J* = 1.6 Hz, olefinic-*H*), 3.70 (2H, s), 2.09 (2H, br t, *J* = 6.4 Hz), 1.90 (2H, br t, *J* = 6.4 Hz), 1.83 (2H, br quintet, *J* = 6.4 Hz), 1.74 (2H, br quintet, *J* = 6.4 Hz), 1.57–1.49 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 169.2 (2 x C, 2 x O-C=O), 152.2 (C), 142.9 (C), 136.9 (C), 130.1 (CH), 127.6 (CH), 125.0 (CH), 121.4 (CH), 106.2 (CH_2, C=*C*H_2), 105.9 (C, O-C-O), 58.5 (C), 40.27 (CH_2), 40.22 (CH_2), 36.2 (CH_2), 23.9 (CH_2), 22.4 (CH_2), 21.7 (CH_2). LRMS m/z 298.65 (M^+), calcd. for $C_{18}H_{18}O_4$ 298.1205; Anal. calcd. for $C_{18}H_{18}O_4$ (298.1205): C, 72.47; H, 6.08; Found C, 72.55; H, 6.12%.

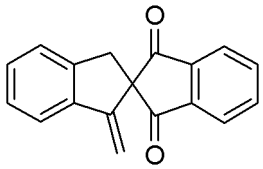


80dh

1',3'-Dimethyl-1-methylenespiro[2,3-dihydro-1*H*-indene-2,5'-(hexahydropyrimidine)]-2',4',6'-trione (80da): Purified by column chromatography using EtOAc/hexane and isolated as a solid. IR (neat): ν_{max} 3744, 1670, 1447, 1419, 1362, 1282, 1114, 1038, 882, 760, 720, 680, 662, 637 and 607 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.43 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.33 (2H, m, Ar-*H*), 7.26 (1H, m, Ar-*H*), 5.63 (1H, d, *J* = 2.0 Hz, olefinic-*H*), 5.01 (1H, d, *J* = 2.0 Hz, olefinic-*H*), 3.77 (2H, s), 3.36 (6H, s, 2 x NC*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 169.3 (2 x C, 2 x N-C=O), 151.5 (C), 151.2 (C), 144.1 (C), 135.9 (C), 130.1 (CH), 127.3 (CH), 124.9 (CH), 121.4 (CH), 104.5 (CH_2), 60.8 (C), 39.0 (CH_2), 29.2 (2 x CH_3, 2 x NCH_3). LRMS m/z 270.60 (M^+), calcd. for $C_{15}H_{14}N_2O_3$ 270.1004; Anal. calcd. for $C_{15}H_{14}N_2O_3$ (270.1004): C, 66.66; H, 5.22; N, 10.36; Found C, 66.71; H, 5.19; N, 10.42%.



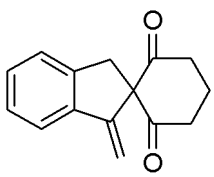
80da



80di

1'-Methylene-2,2'-spirobi[2,3-dihydro-1*H*-indene]-1,3-dione (80di): Purified by column chromatography using EtOAc/hexane and isolated as a solid. IR (neat): ν_{max} 2920, 1729 (C=O), 1703, 1592, 1282, 1256, 1104, 892, 779 and 731 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.12–8.08 (2H, m, Ar-*H*), 7.92–7.88 (2H, m, Ar-*H*), 7.45 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.38–7.31 (2H, m, Ar-*H*), 7.28–7.24 (1H, m, Ar-*H*), 5.54 (1H, d, *J* = 1.6 Hz, olefinic-*H*), 4.45 (1H, d, *J* = 1.6 Hz, olefinic-*H*), 3.48 (2H, s); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 199.5 (2 x C, 2 x C=O), 151.7 (C), 144.0 (C), 143.3 (2 x C), 138.6 (C), 135.8 (2 x CH), 129.8 (CH), 127.2 (CH), 125.2 (CH), 124.2 (2 x CH), 121.0 (CH), 105.1 (CH_2), 64.3 (C), 36.1 (CH_2). LRMS m/z 260.85 (M^+), calcd. for $C_{18}H_{12}O_2$ 260.0837; Anal. calcd. for $C_{18}H_{12}O_2$ (260.0837): C, 83.06; H, 4.65; Found C, 83.11; H, 4.62%.

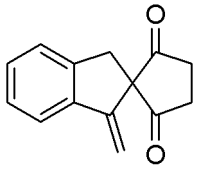
4,4-Dimethyl-1'-methylenespiro[cyclohexane-1,2'-(2',3'-dihydro-1'*H*-indene)]-2,6-dione (80dj): Purified by column chromatography using EtOAc/hexane and isolated as a solid. IR (neat): ν_{max} 2961, 1725 (C=O), 1691 (C=O), 1462, 1329, 1291, 1240, 1112, 781, 732, 642 and 626 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.38 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.31–7.26 (2H, m, Ar-*H*), 7.20 (1H, t, *J* = 8.0 Hz, Ar-*H*), 5.74 (1H, br s, olefinic-*H*), 5.19 (1H, br s, olefinic-*H*), 3.59 (2H, s), 3.01 (2H, d, *J* = 16.0 Hz), 2.61 (2H, d, *J* = 12.0 Hz), 1.21 (3H, s, CH_3), 0.94 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 205.4 (2 x C, 2 x C=O), 149.9 (C), 144.3 (C), 136.8 (C), 129.7 (CH), 127.0 (CH), 124.9 (CH), 121.0 (CH), 105.9 (CH_2), 74.5 (C), 51.8 (2 x CH_2), 36.2 (CH_2), 30.2 (CH_3), 29.9 (C), 27.5 (CH_3). LRMS m/z 254.60 (M^+), calcd. for $C_{17}H_{18}O_2$ 254.1307; Anal. calcd. for $C_{17}H_{18}O_2$ (254.1307): C, 80.28; H, 7.13; Found C, 80.31; H, 7.10%.



80dk

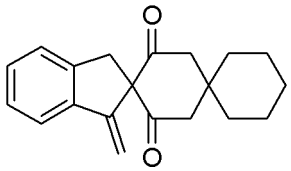
1'-Methylenespiro[cyclohexane-1,2'-(2',3'-dihydro-1'*H*-indene)]-2,6-dione (80dk): Purified by column chromatography using EtOAc/hexane and isolated as a solid. IR (neat): ν_{max} 3849, 2955,

2924, 1717 (C=O), 1689 (C=O), 1265, 1216 and 786 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.38 (1H, d, *J* = 7.6 Hz, Ar-*H*), 7.30–7.25 (2H, m, Ar-*H*), 7.20 (1H, t, *J* = 7.2 Hz, Ar-*H*), 5.76 (1H, br s, olefinic-*H*), 5.21 (1H, br s, olefinic-*H*), 3.58 (2H, s), 3.02 (2H, dABq, *J* = 12.4, 6.0 Hz), 2.77 (2H, td, *J* = 16.0, 4.4 Hz), 2.25–2.16 (1H, m), 2.00–1.85 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 205.5 (2 x C, 2 x C=O), 150.3 (C), 144.0 (C), 136.9 (C), 129.7 (CH), 126.9 (CH), 124.8 (CH), 120.9 (CH), 106.4 (CH_2), 76.2 (C), 37.9 (2 x CH_2), 36.3 (CH_2), 17.2 (CH_2). LRMS m/z 226.70 (M^+), calcd. for $C_{15}H_{14}O_2$ 226.0994; Anal. calcd. for $C_{15}H_{14}O_2$ (226.0994): C, 79.62; H, 6.24; Found C, 79.73; H, 6.19%.



80dl

1'-Methylenespiro[cyclopentane-1,2'-(2',3'-dihydro-1'*H*-indene)]-2,5-dione (80dl): Purified by column chromatography using EtOAc/hexane and isolated as a solid. IR (neat): ν_{max} 3771, 3511, 1720 (C=O), 1416, 1280, 1255, 1212, 765 and 616 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.40 (1H, d, *J* = 7.6 Hz, Ar-*H*), 7.30–7.25 (2H, m, Ar-*H*), 7.23 (1H, d, *J* = 5.6 Hz, Ar-*H*), 5.61 (1H, br s, olefinic-*H*), 4.87 (1H, br s, olefinic-*H*), 3.28 (2H, s), 3.14 (2H, m), 2.82 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 211.5 (2 x C, 2 x C=O), 150.1 (C), 143.8 (C), 137.2 (C), 129.9 (CH), 127.4 (CH), 125.1 (CH), 121.1 (CH), 104.4 (CH_2), 67.9 (C), 36.4 (CH_2), 35.4 (2 x CH_2). LRMS m/z 212.60 (M^+), calcd. for $C_{14}H_{12}O_2$ 212.0837; Anal. calcd. for $C_{14}H_{12}O_2$ (212.0837): C, 79.22; H, 5.70; Found C, 79.31; H, 5.68%.

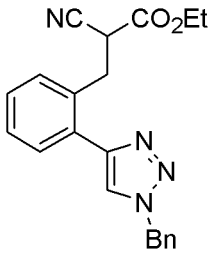


80dm

1"-Methylenedispiro[cyclohexane-1,1'-cyclohexane-4',2"-(2",3"-dihydro-1"*H*-indene)]-3',5'-dione (80dm): Purified by column chromatography using EtOAc/hexane and isolated as a solid. IR (neat): ν_{max} 2930, 2849, 1719 (C=O), 1691 (C=O), 1444, 1333, 1269, 1223, 1096, 1023, 891, 754, 657 and 618 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.40 (1H, d, *J* = 7.6 Hz, Ar-*H*), 7.32–7.27 (2H, m, Ar-*H*), 7.22 (1H, t, *J* = 7.2 Hz, Ar-*H*), 5.76 (1H, d, *J* = 1.2 Hz, olefinic-*H*), 5.22 (1H, d, *J* = 1.2 Hz, olefinic-*H*), 3.59 (2H, s), 2.88 (4H, ABq, *J* = 15.2 Hz), 1.58 (2H, m), 1.55–1.40 (6H, m), 1.25 (2H,

m); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 205.5 (2 x C, 2 x C=O), 150.0 (C), 144.3 (C), 136.9 (C), 129.7 (CH), 127.0 (CH), 124.9 (CH), 121.0 (CH), 106.0 (CH_2), 75.0 (C), 49.6 (2 x CH_2), 38.4 (CH_2), 36.4 (CH_2), 35.8 (CH_2), 32.8 (C), 25.3 (CH_2), 21.3 (CH_2), 21.1 (CH_2). LRMS m/z 295.00 (M^+ +1), calcd. for $C_{20}H_{22}O_2$ 294.16; Anal. calcd. for $C_{20}H_{22}O_2$ (294.16): C, 81.60; H, 7.53; Found C, 81.75; H, 7.49%.

4g. Amino Acid-/$CuSO_4$-/Na-(+)-Ascorbate-Catalyzed Cascade O/H/HC Reactions in One-Pot: In an ordinary glass vial equipped with a magnetic stirring bar, to 0.5 mmol of 2-ethynyl-benzaldehyde **5d**, 0.5 mmol of CH-acid **20** and 0.5 mmol of Hantzsch ester **77a,** was added 1.0 mL of *t*-BuOH and then the catalyst L-proline (0.05 mmol, 10 mol-%, 5.75 mg) was added and the reaction mixture was stirred at 25 °C for 0.5 to 24 h as shown in Table 11. To the crude reaction mixture was added BnN_3 (0.6 mmol, 1.2 equiv., 80 mg), $CuSO_4.5H_2O$ (0.1 mmol, 20 mol-%, 25 mg), Na-(+)-ascorbate (0.2 mmol, 40 mol-%, 40 mg) and H_2O (1.0 mL) and stirred at 25 °C for 2 to 12 h as shown in Table 11. 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 **81** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

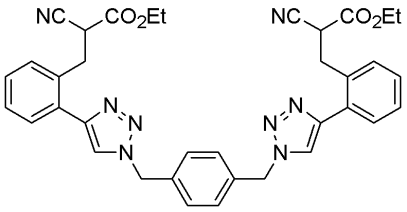


81dba

3-[2-(1-Benzyl-1H-[1,2,3]triazol-4-yl)-phenyl]-2-cyano-propionic acid ethyl ester (81dba): Purified by column chromatography using EtOAc/hexane and isolated as a gummy liquid. IR (neat): ν_{max} 2986, 1744 (O-C=O), 1451, 1369, 1266, 1210, 1104, 1041, 762 and 725 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.66 (1H, s, olefinic-*H*), 7.43–7.35 (5H, m, Ar-*H*), 7.35–7.25 (4H, m, Ar-*H*), 5.57 (2H, s, NC*H*$_2$Ph), 4.48 (1H, dd, *J* = 10.0, 6.4 Hz), 4.22 (1H, q, *J* = 7.2 Hz, $CO_2CH_2CH_3$), 4.20 (1H, q, *J* = 7.2 Hz, $CO_2CH_2CH_3$), 3.66 (1H, dd, *J* = 13.6 and 6.4 Hz), 3.26 (1H, dd, *J* = 13.6 and 10.0 Hz), 1.26 (3H, t, *J* = 7.2 Hz, $CO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 165.9 (C, O-C=O), 147.7 (C), 134.4 (C), 133.8 (C), 131.9 (CH), 129.7 (C), 129.3 (CH), 129.0 (2 x

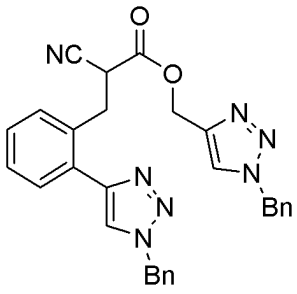
CH), 128.7 (CH), 128.5 (CH), 128.0 (2 x CH), 127.8 (CH), 121.69 (CH), 116.6 (C, CN), 62.5 (CH_2, $CO_2CH_2CH_3$), 54.1 (CH_2, NCH_2Ph), 39.0 (CH), 34.2 (CH_2), 13.8 (CH_3, $CO_2CH_2CH_3$). LRMS m/z 360.85 (M^+), calcd. for $C_{21}H_{20}N_4O_2$ 360.1586; Anal. calcd. for $C_{21}H_{20}N_4O_2$ (360.1586): C, 69.98; H, 5.59; N, 15.55. Found C, 69.88; H, 5.54; N, 15.66%.

2-Cyano-3-{2-[1-(4-{4-[2-(2-cyano-2-ethoxycarbonyl-ethyl)-phenyl]-[1,2,3]triazol-1-ylmethyl}-benzyl)-1H-[1,2,3]triazol-4-yl]-phenyl}-propionic acid ethyl ester (81dbd): Purified by column chromatography using EtOAc/hexane and isolated as a gummy liquid. IR (neat): ν_{max} 3738, 3706, 1741 (O-C=O), 1446, 1263, 1228, 1028, 842, 761, 731 and 636 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.68 (2H, s, 2 x olefinic-*H*), 7.50–7.20 (12H, m, Ar-*H*), 5.60 (4H, s, 2 x NCH_2Ph), 4.44 (2H, dd, *J* = 9.6, 6.0 Hz), 4.23 (2H, q, *J* = 7.2 Hz, $CO_2CH_2CH_3$), 4.20 (2H, q, *J* = 7.2 Hz, $CO_2CH_2CH_3$), 3.65 (2H, dd, *J* = 13.6, 6.0 Hz), 3.28 (2H, dd, *J* = 13.6, 10.0 Hz), 1.28 (6H, t, *J* = 7.2 Hz, 2 x $CO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 165.9 (2 x C, 2 x O-C=O), 147.9 (2 x C), 135.2 (2 x C), 133.9 (2 x C), 131.9 (2 x CH), 129.6 (2 x C), 129.4 (2 x CH), 128.8 (4 x CH), 128.7 (2 x CH), 127.9 (2 x CH), 121.7 (2 x CH), 116.6 (2 x C, 2 x CN), 62.6 (2 x CH_2, 2 x $CO_2CH_2CH_3$), 53.6 (2 x CH_2), 39.1 (2 x CH), 34.2 (2 x CH_2), 13.9 (2 x CH_3, 2 x $CO_2CH_2CH_3$). LRMS m/z 643.45 (M^++1), calcd. for $C_{36}H_{34}N_8O_4$ 642.2703; Anal. calcd. for $C_{36}H_{34}N_8O_4$ (642.2703): C, 67.28; H, 5.33; N, 17.43. Found C, 67.19; H, 5.36; N, 17.51%.



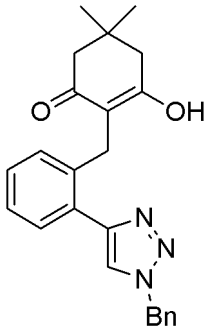
81dbd

3-[2-(1-Benzyl-1H-[1,2,3]triazol-4-yl)-phenyl]-2-cyano-propionic acid 1-benzyl-1H-[1,2,3]triazol-4-ylmethyl ester (81dda): Purified by column chromatography using EtOAc/hexane and isolated as a gummy liquid. IR (neat): ν_{max} 2985, 2249 (C≡N), 1745 (O-C=O), 1606 (C=C), 1454, 1224, 1109, 912 and 723 cm^{-1}; ^1H NMR



81dda

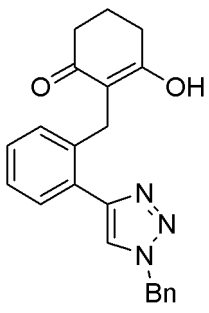
($CDCl_3$) δ 7.64 (1H, br s, olefinic-*H*), 7.58 (1H, br s, olefinic-*H*), 7.45–7.20 (14H, m, Ar-*H*), 5.54 (2H, s, NCH_2Ph), 5.50 (2H, s, NCH_2Ph), 5.27 (2H, s, OCH_2), 4.48 (1H, m), 3.65 (1H, dd, *J* = 13.6, 6.4 Hz), 3.26 (1H, dd, *J* = 13.6, 9.6 Hz); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 165.8 (C, O-C=O), 147.6 (C), 142.1 (C), 134.34 (C), 134.29 (C), 133.5 (C), 131.8 (CH), 129.6 (C), 129.3 (CH), 129.1 (2 x CH), 129.03 (2 x CH), 128.7 (CH), 128.7 (CH), 128.5 (CH), 127.99 (2 x CH), 127.98 (2 x CH), 127.9 (CH), 123.7 (CH), 121.7 (CH), 116.2 (C, CN), 59.5 (CH_2), 54.10 (CH_2), 54.06 (CH_2), 39.0 (CH), 34.3 (CH_2). LRMS m/z 503.55 (M^+), calcd. for $C_{29}H_{25}N_7O_2$ 503.2070; Anal. calcd. for $C_{29}H_{25}N_7O_2$ (503.2070): C, 69.17; H, 5.00; N, 19.47. Found C, 69.23; H, 5.05; N, 19.42%.



81dja

2-[2-(1-Benzyl-1H-[1,2,3]triazol-4-yl)-benzyl]-3-hydroxy-5,5-dimethyl-cyclohex-2-enone (81dja): Purified by column chromatography using EtOAc/hexane and isolated as a solid. IR (neat): ν_{max} 2955, 1595, 1453, 1394, 1331, 1286, 1242, 1154, 1110, 1080, 1045, 990, 817, 765, 724, 637 and 608 cm^{-1}; ^{1}H NMR ($CDCl_3$ + three drops $MeOD_4$) δ 7.76 (1H, d, *J* = 7.2 Hz), 7.49 (1H, d, *J* = 7.6 Hz), 7.42–7.36 (5H, m), 7.30–7.10 (3H, m), 5.61 (2H, s), 3.87 (2H, s), 2.36 (2H, br s), 2.32 (2H, br s), 1.05 (6H, s, 2 x CH_3); ^{13}C NMR ($CDCl_3$ + three drops $MeOD_4$, DEPT–135) δ 199.9 (C, C=O), 174.2 (C), 148.0 (C), 139.6 (C), 133.8 (C), 130.9 (CH), 129.0 (2 x CH), 129.0 (CH), 128.8 (CH), 128.7 (CH), 128.1 (2 x CH), 126.6 (C), 125.9 (CH), 122.0 (CH), 113.3 (C), 54.5 (CH_2), 50.4 (CH_2), 43.6 (CH_2), 31.6 (C), 27.9 (2 x CH_3), 23.8 (CH_2). LRMS m/z 388.55 (M^+ + 1), calcd. for $C_{24}H_{25}N_3O_2$ 387.1947; Anal. calcd. for $C_{24}H_{25}N_3O_2$ (387.1947): C, 74.39; H, 6.50; N, 10.84. Found C, 74.45; H, 6.54; N, 10.79%.

2-[2-(1-Benzyl-1H-[1,2,3]triazol-4-yl)-benzyl]-3-hydroxy-cyclohex-2-enone

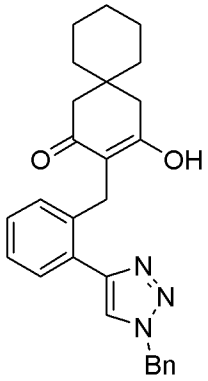


81dka

(81dka): Purified by column chromatography using EtOAc/hexane and isolated as a solid. IR (neat): ν_{max} 1595, 1329, 1285, 1240, 1110,

1079, 1051, 818, 765, 715 and 663 cm^{-1}; ^1H NMR ($CDCl_3$ + three drops $MeOD_4$) δ 7.65 (1H, br s), 7.56 (1H, d, *J* = 7.6 Hz), 7.45–7.30 (4H, m), 7.30–7.20 (2H, m), 7.20–7.10 (2H, m), 5.59 (2H, s), 3.89 (2H, s), 2.49–2.43 (4H, m), 1.93 (2H, m); ^{13}C NMR ($CDCl_3$ + three drops $MeOD_4$, DEPT–135) δ 200.0 (C, *C*=O), 175.8 (C), 148.2 (C), 139.9 (C), 133.8 (C), 131.4 (CH), 129.2 (3 x CH), 129.0 (CH), 128.6 (CH), 128.2 (2 x CH), 126.6 (C), 126.0 (CH), 121.9 (CH), 114.7 (C), 54.6 (CH_2), 36.8 (CH_2), 30.0 (CH_2), 24.0 (CH_2), 20.7 (CH_2). LRMS m/z 359.60 (M^+), calcd. for $C_{22}H_{21}N_3O_2$ 359.1634; Anal. calcd. for $C_{22}H_{21}N_3O_2$ (359.1634): C, 73.52; H, 5.89; N, 11.69. Found C, 73.58; H, 5.86; N, 11.62%.

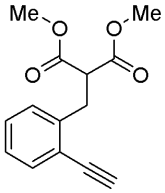
3-[2-(1-Benzyl-1H-[1,2,3]triazol-4-yl)-benzyl]-4-hydroxy-spiro[5.5]undec-3-en-2-one (81dma): Purified by column chromatography using EtOAc/hexane and isolated as a solid. IR (neat): ν_{max} 2926, 2854, 1596, 1447, 1398, 1266, 1232, 1110, 910, 801, 758, 695, 645 and 614 cm^{-1}; ^1H NMR ($CDCl_3$ + three drops $MeOD_4$) δ 7.73–7.70 (1H, m), 7.50 (1H, d, *J* = 7.6 Hz), 7.45–7.30 (5H, m), 7.30–7.10 (3H, m), 5.61 (2H, br s), 3.86 (2H, s), 2.42 (2H, s), 2.39 (2H, s), 1.45 (10H, m); ^{13}C NMR ($CDCl_3$ + three drops $MeOD_4$, DEPT–135) δ 199.7 (C, *C*=O), 173.8 (C), 148.1 (C), 139.7 (C), 133.8 (C), 131.2 (CH), 129.1 (3 x CH), 128.9 (CH), 128.7 (CH), 128.1 (2 x CH), 126.6 (C), 125.9 (CH), 122.1 (CH), 113.3 (C), 54.5 (CH_2), 48.6 (CH_2), 41.1 (CH_2), 36.4 (2 x CH_2), 34.3 (C), 26.0 (CH_2), 23.9 (CH_2), 21.5 (2 x CH_2). LRMS m/z 428.00 (M^+ + 1), calcd. for $C_{27}H_{29}N_3O_2$ 427.2260; Anal. calcd. for $C_{27}H_{29}N_3O_2$ (427.2260): C, 75.85; H, 6.84; N, 9.83. Found C, 75.89; H, 6.81; N, 9.88%.



81dma

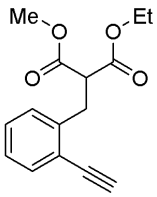
4c. Amino Acid-Catalyzed Cascade O/H/A/K/E Reactions in One-Pot: In an ordinary glass vial equipped with a magnetic stirring bar, to 1.0 mmol of 2-ethynyl-benzaldehyde **5d**, 0.5 mmol of Meldrum's acid **20g** and 0.5 mmol of *o*-phenylenediamine **82,** was added 1.7 mL of solvent and then the catalyst L-proline (0.1 mmol, 20 mol-%, 11.5 mg) was added and the reaction mixture was stirred at 25 °C for

the time indicated in Table 12. To the crude reaction mixture 15 equiv. of an ethereal solution of diazomethane was added and the reaction mixture was stirred at room temperature for the time indicated in Table 12. After evaporation of the solvent and excess diazomethane completely in fume hood, the crude reaction mixture was directly loaded onto a silica gel column with or without aqueous work-up and pure one-pot products **79** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).



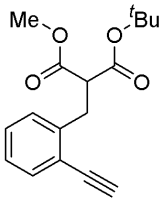
79dga

2-(2-Ethynyl-benzyl)-malonic acid dimethyl ester (79dga): Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 3730, 3286, 1736 (O-C=O), 1439, 1344, 1297, 1234, 1154, 1024, 764 and 603 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.46 (1H, br d, *J* = 6.8 Hz), 7.30–7.15 (3H, m) [Ar-*H*]; 3.92 (1H, t, *J* = 8.0 Hz), 3.67 (6H, s, 2 x O*C*H_3), 3.38 (2H, d, *J* = 8.0 Hz), 3.32 (1H, s, Ar-C≡C*H*); ^{13}C NMR ($CDCl_3$, DEPT−135) δ 169.2 (C, 2 x O-C=O), 140.1 (C), 133.1 (CH), 129.7 (CH), 128.9 (CH), 126.9 (CH), 121.8 (C), 82.0 (CH, Ar-C≡*C*H), 81.5 (C, Ar-*C*≡CH), 52.5 (CH_3, 2 x O*C*H_3), 51.9 (CH), 33.5 (CH_2, *C*H_2Ar); LCMS: m/z 247.00 ($M + H^+$), calcd. $C_{14}H_{14}O_4$ 246.09; Anal. calcd. for $C_{14}H_{14}O_4$ (246.09): C, 68.28; H, 5.73. Found: C, 68.33; H, 5.69%.



79dgb

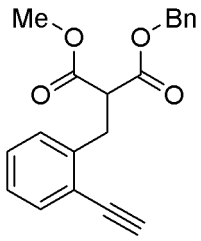
2-(2-Ethynyl-benzyl)-malonic acid ethyl ester methyl ester (79dgb): Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 2953, 1737 (O-C=O), 1440, 1347, 1296, 1230, 1152, 758, 692 and 642 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.47 (1H, d, *J* = 8.0 Hz), 7.30–7.15 (3H, m) [Ar-*H*]; 4.14 (2H, q, *J* = 7.2 Hz, O*C*H_2CH$_3$), 3.91 (1H, t, *J* = 8.0 Hz), 3.69 (3H, s, O*C*H_3), 3.38 (2H, d, *J* = 8.0 Hz), 3.32 (1H, s, Ar-C≡C*H*), 1.20 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT−135) δ 169.3 (C, O-C=O), 168.8 (C, O-C=O), 140.2 (C), 133.0 (CH), 129.7 (CH), 128.9 (CH), 126.8 (CH), 121.9 (C), 81.9 (CH, Ar-C≡*C*H), 81.5 (C, Ar-*C*≡CH), 61.5 (CH_2, O*C*H$_2$CH$_3$),



79dgi

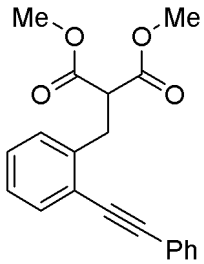
52.4 (CH_3, O*C*H_3), 52.0 (CH), 33.5 (CH_2, *C*H_2Ar), 14.0 (CH_3, OCH$_2$*C*H_3); LCMS: m/z 261.00 (M + H^+), calcd. $C_{15}H_{16}O_4$ 260.10; Anal. calcd. for $C_{15}H_{16}O_4$ (260.10): C, 69.22; H, 6.20. Found: C, 69.28; H, 6.17%.

2-(2-Ethynyl-benzyl)-malonic acid tert-butyl ester methyl ester (79dgi): Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 3729, 3286, 2973, 1729 (O-C=O), 1442, 1368, 1297, 1241, 1145, 841 and 673 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.47 (1H, d, *J* = 7.6 Hz), 7.30–7.15 (3H, m) [Ar-*H*]; 3.82 (1H, t, *J* = 7.6 Hz), 3.69 (3H, s, OC*H*$_3$), 3.35 (2H, d, *J* = 7.6 Hz), 3.31 (1H, s, Ar-C≡C*H*), 1.38 (9H, s, O-C(C*H*$_3$)$_3$); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 169.7 (C, O-C=O), 167.9 (C, O-C=O), 140.5 (C), 133.0 (CH), 129.8 (CH), 128.8 (CH), 126.7 (CH), 121.9 (C), 81.9 (C, O-*C*(CH$_3$)$_3$), 81.8 (CH, Ar-C≡*C*H), 81.6 (C, Ar-*C*≡CH), 52.9 (CH_3, O*C*H$_3$), 52.3 (CH), 33.5 (CH_2, *C*H$_2$Ar), 27.8 (CH_3, OC(*C*H$_3$)$_3$); LCMS: m/z 289.00 (M + H^+), calcd. $C_{17}H_{20}O_4$ 288.14; Anal. calcd. for $C_{17}H_{20}O_4$ (288.14): C, 70.81; H, 6.99. Found: C, 70.76; H, 6.93%.



79dgf

2-(2-Ethynyl-benzyl)-malonic acid benzyl ester methyl ester (79dgf): Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 3285, 2973, 1731 (O-C=O), 1436, 1245, 1170, 1055, 784 and 735 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.48 (1H, br d, *J* = 7.6 Hz), 7.37–7.30 (3H, m), 7.28–7.15 (5H, m) [Ar-*H*]; 5.14 (2H, br s, OC*H*$_2$Ph), 4.00 (1H, t, *J* = 8.0 Hz), 3.68 (3H, s, OC*H*$_3$), 3.42 (2H, dd, *J* = 7.6, 4.0 Hz), 3.30 (1H, s, Ar-C≡C*H*); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 169.1 (C, O-C=O), 168.7 (C, O-C=O), 140.0 (C), 135.4 (C), 133.0 (CH), 129.8 (CH), 128.9 (CH), 128.5 (2 x CH), 128.3 (CH), 128.0 (2 x CH), 126.9 (CH), 121.8 (C), 82.0 (CH, Ar-C≡*C*H), 81.5 (C, Ar-*C*≡CH), 67.1 (CH_2, O*C*H$_2$Ph), 52.5 (CH), 52.1 (CH_3, O*C*H$_3$), 33.5 (CH_2, *C*H$_2$Ar); LCMS: m/z 323.00 (M+H^+), calcd. $C_{20}H_{18}O_4$ 322.12.



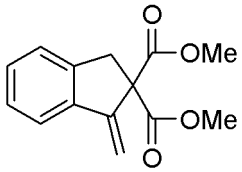
79aga

2-(2-Phenylethynyl-benzyl)-malonic acid dimethyl ester (79aga): Purified by column chromatography using EtOAc/hexane and isolated

as oil. IR (neat): ν_{max} 2952, 1737 (O-C=O), 1494, 1440, 1347, 1295, 1231, 1152, 1026, 758 and 688 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.65–7.55 (3H, m), 7.45–7.36 (3H, m), 7.35–7.25 (3H, m) [Ar-*H*]; 4.07 (1H, t, *J* = 7.6 Hz), 3.74 (6H, s, 2 x O*C*H_3), 3.52 (2H, d, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 169.2 (2 x C, 2 x O-C=O), 139.5 (C), 132.2 (CH), 131.5 (2 x CH), 129.9 (CH), 128.4 (CH), 128.35 (CH), 128.30 (2 x CH), 126.9 (CH), 123.0 (C), 122.8 (C), 94.2 (C), 87.1 (C), 52.4 (2 x CH_3, 2 x O*C*H_3), 52.1 (CH), 33.9 (CH_2, *C*H_2Ar); LCMS: m/z 323.00 ($M+H^+$), calcd. $C_{20}H_{18}O_4$ 322.12; Anal. calcd. for $C_{20}H_{18}O_4$ (322.12): C, 74.52; H, 5.63. Found: C, 74.68; H, 5.60%.

4f. Amino Acid-/CuI-/Base-Catalyzed Cascade O/H/A/K/E/CC Reactions in One-Pot: In an ordinary glass vial equipped with a magnetic stirring bar, to 1.0 mmol of 2-ethynyl-benzaldehyde **5d**, 0.5 mmol of Meldrum's acid **20g** and 0.5 mmol of *o*-phenylenediamine **82,** was added 1.7 mL of solvent and then the catalyst L-proline (0.1 mmol, 20 mol-%, 11.5 mg) was added and the reaction mixture was stirred at 25 °C for the time indicated in Table 12. To the crude reaction mixture 15 equiv. of an ethereal solution of diazomethane was added and the reaction mixture was stirred at room temperature for the time indicated in Table 12. After evaporation of the solvent and excess diazomethane completely in fume hood, CuI (0.1 mmol, 20 mol-%, 19 mg), *t*-BuOK (0.5 mmol, 1 equiv., 56 mg) and THF (3.0 mL) were added to the crude reaction mixture and stirred at 25 °C for 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 cascade products **80** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

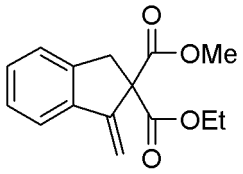
1-Methylene-indan-2,2-dicarboxylic acid dimethyl ester (80dga): Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 3501, 3473, 3403, 1732 (O-C=O), 1642, 1436, 1251, 1195, 1171, 1057 and 761 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.49



80dga

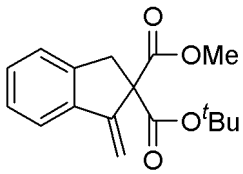
(1H, d, *J* = 6.4 Hz), 7.28–7.20 (3H, m) [Ar-*H*]; 5.87 (1H, s, olefinic-*H*), 5.54 (1H, s, olefinic-*H*), 3.77 (6H, s, 2 x OC*H*$_3$), 3.71 (2H, s); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 170.7 (2 x C, 2 x O-C=O), 146.6 (C), 141.8 (C), 138.5 (C), 129.2 (CH), 127.2 (CH), 124.8 (CH), 120.9 (CH), 109.4 (CH_2, C=*C*H_2), 63.4 (C), 53.1 (2 x CH_3, 2 x O*C*H_3), 39.9 (CH_2, *C*H_2Ar); LCMS: m/z 247.00 (M+H$^+$), calcd. $C_{14}H_{14}O_4$ 246.09; Anal. calcd. for $C_{14}H_{14}O_4$ (246.09): C, 68.28; H, 5.73. Found: C, 68.15; H, 5.77%.

1-Methylene-indan-2,2-dicarboxylic acid ethyl ester methyl ester (80dgb): Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 3993, 3729, 2962, 1732 (O-C=O), 1291, 1248, 1173, 1054, 1018 and 797 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.48 (1H, d, *J* = 6.8 Hz), 7.26–7.21 (3H, m) [Ar-*H*]; 5.87 (1H, s, olefinic-*H*), 5.54 (1H, s, olefinic-*H*), 4.24 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 3.77 (3H, s, OC*H*$_3$), 3.70 (2H, d, *J* = 3.2 Hz), 1.25 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 170.8 (C, O-C=O), 170.1 (C, O-C=O), 146.6 (C), 141.9 (C), 138.6 (C), 129.2 (CH), 127.2 (CH), 124.8 (CH), 120.9 (CH), 109.4 (CH_2, C=*C*H_2), 63.4 (C), 62.0 (CH_2, O*C*H_2CH$_3$), 53.0 (CH_3, O*C*H_3), 39.8 (CH_2, *C*H_2Ar), 14.0 (CH_3, OCH$_2$*C*H_3); LCMS: m/z 261.00 (M+H$^+$), calcd. $C_{15}H_{16}O_4$ 260.10; Anal. calcd. for $C_{15}H_{16}O_4$ (260.10): C, 69.22; H, 6.20. Found: C, 69.18; H, 6.23%.



80dgb

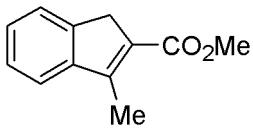
1-**Methylene-indan-2,2-dicarboxylic acid tert-butyl ester methyl ester (80dgi):** Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 1731 (O-C=O), 1369, 1290, 1252, 1150, 1055, 845,794, 728 and 646 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.48 (1H, d, *J* = 6.4 Hz), 7.26–7.19 (3H, m) [Ar-*H*]; 5.87 (1H, s, olefinic-*H*), 5.54 (1H, s, olefinic-*H*), 3.77 (3H, s, OC*H*$_3$), 3.65 (2H, ABq, *J* = 17.2 Hz), 1.46 (9H, s, O-C(C*H*$_3$)$_3$); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 171.1 (C, O-C=O), 168.9 (C, O-C=O), 146.7 (C), 142.0 (C), 138.7 (C), 129.1 (CH), 127.1 (CH), 124.8 (CH), 120.8 (CH), 109.2 (CH_2, C=*C*H_2), 82.2 (C, O-*C*(CH$_3$)$_3$), 64.2 (C), 52.8 (CH_3, O*C*H_3),



80dgi

39.7 (CH_2, *C*H_2Ar), 27.8 (CH_3, O-C(*C*H_3)$_3$); LCMS: m/z 289.00 (M + H^+), calcd. $C_{17}H_{20}O_4$ 288.14; Anal. calcd. for $C_{17}H_{20}O_4$ (288.14): C, 70.81; H, 6.99. Found: C, 70.86; H, 7.06%.

1-**Methylene-indan-2,2-dicarboxylic acid benzyl ester methyl ester (80dgf):** Purified by column chromatography using EtOAc/hexane and isolated as oil. IR (neat): ν_{max} 1732 (O-C=O), 1436, 1245, 1170, 1054, 784, 735 and 660 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.45 (1H, d, *J* = 6.4 Hz), 7.30–7.19 (5H, m), 7.20–7.10 (3H, m) [Ar-*H*]; 5.78 (1H, s, olefinic-*H*), 5.45 (1H, s, olefinic-*H*), 5.14 (2H, OC*H*$_2$Ph), 3.64 (3H, s, OC*H*$_3$), 3.63 (2H, s); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 170.6 (C, O-C=O), 169.9 (C, O-C=O), 146.3 (C), 141.7 (C), 138.5 (C), 135.4 (C), 129.2 (CH), 128.5 (2 x CH), 128.2 (CH), 127.9 (2 x CH), 127.2 (CH), 124.8 (CH), 120.9 (CH), 109.6 (CH_2, C=*C*H_2), 67.5 (CH_2, OCH_2Ph), 63.5 (C), 52.9 (CH_3, OCH_3), 39.8 (CH_2, *C*H_2Ar); LCMS: m/z 321.00 (M - H^+), calcd. $C_{20}H_{18}O_4$ 322.12.

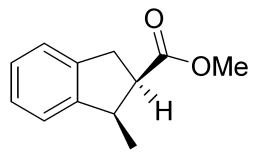


80dgf

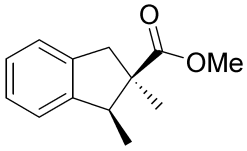
3-Methyl-1*H*-indene-2-carboxylic acid methyl ester (83dg): Purified by column chromatography using EtOAc/hexane and isolated as a white solid; IR (neat) ν_{max} 2360, 2335, 1705 (O-C=O), 1606, 1574, 1434, 1386, 1327, 1245, 1192, 1124 and 1067 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.49 (2H, br s), 7.36 (2H, br s) [Ar-*H*], 3.83 (3H, s, OC*H*$_3$), 3.65 (2H, s, C*H*$_2$), 2.55 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT–135) δ □166.3 (C, O-*C*=O), 151.7 (C), 145.2 (C), 143.4 (C), 129.4 (C), 127.7 (CH), 126.5 (CH), 124.0 (CH), 121.1 (CH), 51.2 (CH_3, CO_2*C*H_3), 38.7 (CH_2), 12.4 (CH_3); LRMS m/z 188.75 (M^+), calcd. for $C_{12}H_{12}O_2$ 188.0837; Anal. calcd. for $C_{12}H_{12}O_2$ (188.0837): C, 76.57; H, 6.43. Found C, 76.45; H, 6.51%.

83dg

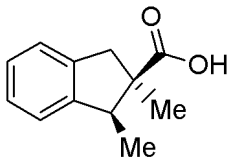
1-Methyl-indan-2-carboxylic acid methyl ester : Purified by column chromatography using EtOAc/hexane and isolated as a liquid. IR (neat) ν_{max} 2953, 1735 (O-C=O), 1477, 1455, 1438, 1363, 1257, 1225, 1193, 1175,



1043, 1017 and 829 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.23–7.19 (4H, m, Ar-*H*), 3.74 (3H, s, OC*H*$_3$), 3.56 (1H, quintet, *J* = 7.6 Hz, C*H*CH_3), 3.48–3.36 (2H, m, C*H*$_2$), 3.00 (1H, dd, *J* = 14.8, 6.8 Hz, C*H*CO_2Me), 1.13 (3H, d, *J* = 6.8 Hz, CHC*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 174.2 (C, O-*C*=O), 146.8 (C), 140.9 (C), 126.8 (CH), 126.7 (CH), 124.5 (CH), 123.5 (CH), 51.5 (CH_3, O*C*H_3), 48.4 (CH), 41.8 (CH), 33.0 (CH_2), 17.0 (CH_3, CH*C*H_3); LRMS m/z 188.95 (M^+ - 1), calcd. for $C_{12}H_{14}O_2$ 190.0994; Anal. calcd. for $C_{12}H_{14}O_2$ (190.0994): C, 75.76; H, 7.42. Found C, 75.68; H, 7.47%.



1,2-Dimethyl-indan-2-carboxylic acid methyl ester: Purified by column chromatography using EtOAc/hexane and isolated as a liquid; IR (neat) ν_{max} 2962, 1730 (O-C=O), 1457, 1440, 1374 1299, 1252, 1231, 1199, 1116 and 1074 cm^{-1}; ^1H NMR ($CDCl_3$, 13:1 ratio of isomers, major isomer) δ 7.19–7.14 (4H, m, Ar-*H*), 3.70 (3H, s, OC*H*$_3$), 3.63 (1H, d, *J* = 16.0 Hz), 3.08 (1H, q, *J* = 7.2 Hz, C*H*CH_3), 2.68 (1H, d, *J* = 16.0 Hz), 1.34 (3H, s, C*H*$_3$), 1.11 (3H, d, *J* = 7.2 Hz, CHC*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT–135, 13:1 ratio of isomers, major isomer) δ 176.5 (C, O-*C*=O), 146.4 (C), 140.7 (C), 126.7 (CH), 126.6 (CH), 124.8 (CH), 123.9 (CH), 53.8 (C), 51.6 (CH_3, O*C*H_3), 50.1 (CH, *C*HCH_3), 41.0 (CH_2), 25.0 (CH_3), 17.5 (CH_3); LRMS m/z 205.10 (M^+ + 1), calcd. for $C_{13}H_{16}O_2$ 204.1150; Anal. calcd. for $C_{13}H_{16}O_2$ (204.1150): C, 76.44; H, 7.90. Found C, 76.51; H, 7.85%.



84dg

1,2-Dimethyl-indan-2-carboxylic acid (84dg): Isolated as a white solid from aqueous workup; IR (neat) ν_{max} 2964, 1690 (O-C=O), 1460, 1413, 1322, 1297, 1267, 1240, 1212, 1131 and 961 cm^{-1}; ^1H NMR ($CDCl_3$, 12:1 ratio of isomers, major isomer) δ 8.99 (1H, br s, CO_2*H*), 7.20–7.16 (4H, m, Ar-*H*), 3.63 (1H, d, *J* = 16.0 Hz), 3.15 (1H, q, *J* = 7.2 Hz, C*H*CH_3), 2.73 (1H, d, *J* = 16.0 Hz), 1.41 (3H, s, C*H*$_3$), 1.25 (3H, d, *J* = 6.8 Hz, CHC*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT–135, 12:1 ratio of isomers, major isomer) δ 182.6 (C, O-*C*=O), 146.2 (C), 140.7 (C), 126.8 (CH), 126.6 (CH), 124.7 (CH), 123.9 (CH),

53.8 (C), 49.8 (CH, *C*HCH$_3$), 40.9 (CH$_2$), 24.9 (CH$_3$), 17.3 (CH$_3$); LRMS m/z 189.00 (M-1), calcd. for $C_{12}H_{14}O_2$ 190.0994; Anal. calcd. for $C_{12}H_{14}O_2$ (190.0994): C, 75.76; H, 7.42. Found C, 75.68; H, 7.51%.

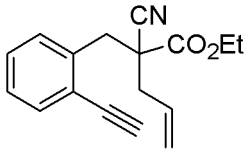
5. General Experimental Procedures for the Multi-catalysis Reactions:

5a. **Amino acid-/Self-/K_2CO_3-Catalyzed Cascade Three-component Reductive Alkylation (TCRA)/C-Allylation (C-A) Reactions: Method-A:** In an ordinary glass vial equipped with a magnetic stirring bar, to 0.3 mmol of 2-ethynyl-benzaldehyde **5d** and 0.3 mmol of CH-acid **20,** was added 1.2 mL of solvent and then the catalyst L-proline (0.06 mmol, 20 mol-%, 6.9 mg) was added and the reaction mixture was stirred at 25 °C for 3 to 16 h, then o-phenylenediamine **82** (0.3 mmol) and benzaldehyde (0.3 mmol) were added and stirred for 3 to 16 h. To the crude reaction mixture was added 5 equiv. of allyl bromide (1.5 mmol, 180 mg) and 8 equiv. of K_2CO_3 (2.4 mmol, 331 mg) and the reaction mixture was stirred at 25 °C for 0.25 to 12 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 TCRA/*C*-A products **90** were obtained by column chromatography (silica gel, mixture of hexane/ ethylacetate).

Amino acid-/Self-/K_2CO_3-Catalyzed Cascade Three-component Reductive Alkylation (TCRA)/C-Allylation (C-A) Reactions: Method-B: In an ordinary glass vial equipped with a magnetic stirring bar, to 0.3 mmol of 2-ethynyl-benzaldehyde **5d**, 0.3 mmol of CH-acid **20** and 0.3 mmol of Hantzsch ester **77a,** was added 1.2 mL of solvent and then the catalyst L-proline (0.06 mmol, 20 mol-%, 6.9 mg) was added and the reaction mixture was stirred at 25 °C for 0.75 to 24 h. To the crude reaction mixture was added 5 equiv. of allyl bromide (1.5 mmol, 180 mg) and 8 equiv. of K_2CO_3 (2.4 mmol, 331 mg) and the reaction mixture was stirred at 25 °C for 0.25 to 1 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 TCRA/*C*-A products **90** were obtained by column chromatography (silica gel, mixture of hexane/ ethylacetate).

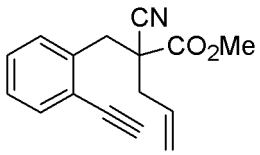
Amino acid-/Self-/Self-/Self-/Self-/K_2CO_3-Catalyzed Cascade TCRA/A/K/E/C-A Reactions in One-Pot: Method-C: In an ordinary glass vial equipped with a magnetic stirring bar, to 0.3 mmol of 2-ethynyl-benzaldehyde **5d**, 0.3 mmol of Meldrum's acid **20g** and 0.3 mmol of Hantzsch ester **77a,** was added 1.2 mL of solvent (R-OH) and then the catalyst L-proline (0.06 mmol, 20 mol-%, 6.9 mg) was added and the reaction mixture was stirred at 25 °C for 1 h. To the crude reaction mixture 15 equiv. of an ethereal solution of diazomethane was added and the reaction mixture was stirred at room temperature for the time indicated in Table 13. After evaporation of the solvent and excess diazomethane completely in fume hood, DMSO (1.2 mL) was added to the crude reaction mixture followed by 5 equiv. of allyl bromide (1.5 mmol, 180 mg) and 6 equiv. of K_2CO_3 (1.8 mmol, 248 mg) and the reaction mixture was stirred at 25 °C for 12 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 TCRA/A/K/E/*C*-A products **91** were obtained by column chromatography (silica gel, mixture of hexane/ ethylacetate).



90db

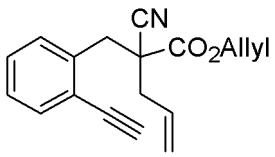
2-Cyano-2-(2-ethynyl-benzyl)-pent-4-enoic acid ethyl ester (90db): Purified by column chromatography using EtOAc/hexane and isolated as a liquid; IR (neat) ν_{max} 3271, 2985, 1740 (O-C=O), 1480, 1444, 1369, 1330, 1291, 1226, 1144, 1103, 1048, 997, 932, 860, 763, 660 and 632 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.52 (1H, d, *J* = 7.6 Hz), 7.40 (1H, d, *J* = 7.6 Hz), 7.33 (1H, br t, *J* = 7.6 Hz), 7.26 (1H, br t, *J* = 7.6 Hz) [Ar-*H*]; 5.87–5.81 (1H, m, CH_2CH=CH_2), 5.29–5.23 (2H, m, CH_2CH=CH_2), 4.21 (2H, q, *J* = 7.2 Hz, $CO_2CH_2CH_3$), 3.50 (1H, d, *J* = 14.0 Hz), 3.39 (1H, d, *J* = 14.0 Hz), 3.31 (1H, s, Ar-C≡C-*H*), 2.84 (1H, dd, *J* = 14.0, 7.6 Hz, CH_2CH=CH_2), 2.55 (1H, dd, *J* = 14.0, 7.2 Hz, CH_2CH=CH_2), 1.22 (3H, t, *J* = 7.2 Hz, $CO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$, DEPT–135)

δ: 168.0 (C, O-*C*=O), 136.6 (C), 133.3 (CH), 130.8 (CH), 129.9 (CH), 129.0 (CH), 127.7 (CH), 123.2 (C), 120.9 (CH_2, CH_2CH=*C*H_2), 118.4 (C, *C*N), 82.0 (CH, Ar-C≡*C*-H), 81.9 (C, Ar-*C*≡C-H), 62.9 (CH_2, CO_2*C*H_2CH_3), 50.6 (C), 40.8 (CH_2), 39.6 (CH_2, *C*H_2CH=CH_2), 13.9 (CH_3, CO_2CH_2*C*H_3).; LRMS m/z 268.15 (M+1), calcd. for $C_{17}H_{17}NO_2$ 267.1259; Anal. calcd. for $C_{17}H_{17}NO_2$ (267.1259): C, 76.38; H, 6.41; N, 5.24, Found C, 76.21; H, 6.44; N, 5.35%.



90dn

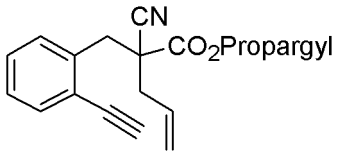
2-Cyano-2-(2-ethynyl-benzyl)-pent-4-enoic acid methyl ester (90dn): Purified by column chromatography using EtOAc/hexane and isolated as a liquid; IR (neat) ν_{max} 3272, 2956, 1745 (O-C=O), 1644, 1481, 1440, 1332, 1276, 1236, 1143, 1106, 1050, 993, 931, 763, 665, 656 and 621 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.52 (1H, d, *J* = 7.2 Hz), 7.38–7.25 (3H, m) [Ar-*H*]; 5.88–5.77 (1H, m, CH_2CH=CH_2), 5.29–5.23 (2H, m, CH_2CH=C*H*$_2$), 3.75 (3H, s, CO_2CH_3), 3.50 (1H, d, *J* = 13.6 Hz), 3.39 (1H, d, *J* = 14.0 Hz), 3.31 (1H, s, Ar-C≡C-*H*), 2.83 (1H, dd, *J* = 14.0, 7.6 Hz, C*H*$_2$CH=CH_2), 2.55 (1H, dd, *J* = 14.0, 7.2 Hz, C*H*$_2$CH=CH_2); ^{13}C NMR ($CDCl_3$, DEPT–135) δ: 168.5 (C, O-*C*=O), 136.4 (C), 133.2 (CH), 130.7 (CH), 129.9 (CH), 129.0 (CH), 127.7 (CH), 123.1 (C), 121.0 (CH_2, CH_2CH=*C*H_2), 118.2 (C, *C*N), 81.9 (CH, Ar-C≡*C*-H), 81.8 (C, Ar-*C*≡C-H), 53.3 (CH_3, CO_2*C*H_3), 50.6 (C), 40.7 (CH_2), 39.6 (CH_2, *C*H_2CH=CH_2).; LRMS m/z 254.10 (M^+ + 1), calcd. for $C_{16}H_{15}NO_2$ 253.1103; Anal. calcd. for $C_{16}H_{15}NO_2$ (253.1103): C, 75.87; H, 5.97; N, 5.53, Found C, 75.81; H, 6.03; N, 5.61%.



90do

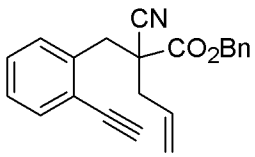
2-Cyano-2-(2-ethynyl-benzyl)-pent-4-enoic acid allyl ester (90do): Purified by column chromatography using EtOAc/hexane and isolated as a liquid; IR (neat) ν_{max} 3285, 1744 (O-C=O), 1645, 1483, 1444, 1365 1272, 1215, 1143, 1107, 994, 933, 763, 660 and 603 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.52 (1H, dd, *J* = 8.0, 1.2 Hz), 7.40 (1H, br d, *J* = 7.6 Hz), 7.33 (1H, dt, *J* = 8.0, 1.6 Hz), 7.26 (1H, dt, *J* = 8.0, 1.6 Hz)

[Ar-*H*]; 5.89–5.78 (2H, m, CH_2CH=CH_2, CO_2CH_2CH=CH_2), 5.33–5.22 (4H, m, CH_2CH=CH_2, CO_2CH_2CH=CH_2), 4.64 (2H, d, *J* = 6.0 Hz, CO_2CH_2CH=CH_2), 3.52 (1H, d, *J* = 13.6 Hz), 3.41 (1H, d, *J* = 14.0 Hz), 3.31 (1H, s, Ar-C≡C-*H*), 2.85 (1H, dd, *J* = 14.0, 7.6 Hz, CH_2CH=CH_2), 2.56 (1H, dd, *J* = 14.0, 7.2 Hz, CH_2CH=CH_2); ^{13}C NMR ($CDCl_3$, DEPT–135) δ: 167.8 (C, O-*C*=O), 136.5 (C), 133.3 (CH), 130.74 (CH), 130.67 (CH), 130.0 (CH), 129.1 (CH), 127.8 (CH), 123.2 (C), 121.1 (CH_2, CH_2CH=CH_2), 119.4 (CH_2, CO_2CH_2CH=CH_2), 118.2 (C, *C*N), 82.0 (CH, Ar-C≡*C*-H), 81.9 (C, Ar-*C*≡C-H), 67.1 (CH_2, CO_2CH_2CH=CH_2), 50.7 (C), 40.8 (CH_2), 39.7 (CH_2, CH_2CH=CH_2).; LRMS m/z 280.0 (M^+ + 1), calcd. for $C_{18}H_{17}NO_2$ 279.1259; Anal. calcd. for $C_{18}H_{17}NO_2$ (279.1259): C, 77.40; H, 6.13; N, 5.01, Found C, 77.51; H, 6.10; N, 5.08%.



90dd

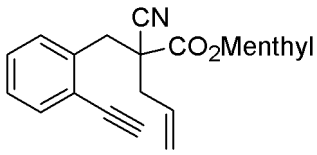
2-Cyano-2-(2-ethynyl-benzyl)-pent-4-enoic acid prop-2-ynyl ester (90dd): Purified by column chromatography using EtOAc/hexane and isolated as a liquid; IR (neat) ν_{max} 3291, 1751 (O-C=O), 1645, 1483, 1442, 1370, 1272, 1204, 1140, 1106, 1045, 996, 930, 764, 678 and 649 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 7.53 (1H, d, *J* = 7.4 Hz), 7.41 (1H, d, *J* = 7.6 Hz), 7.34 (1H, br t, *J* = 7.6 Hz), 7.28 (1H, br t, *J* = 8.0 Hz) [Ar-*H*]; 5.90–5.79 (1H, m, CH_2CH=CH_2), 5.30–5.25 (2H, m, CH_2CH=CH_2), 4.75 (2H, d, *J* = 2.2 Hz, CO_2CH_2C≡C-H), 3.53 (1H, d, *J* = 13.9 Hz), 3.42 (1H, d, *J* = 13.9 Hz), 3.32 (1H, s, Ar-C≡C-*H*), 2.88 (1H, dd, *J* = 13.8, 7.3 Hz, CH_2CH=CH_2), 2.58 (1H, dd, *J* = 13.8, 7.2 Hz, CH_2CH=CH_2), 2.51 (1H, t, *J* = 2.4 Hz, CO_2CH_2C≡C-*H*); ^{13}C NMR ($CDCl_3$, DEPT–135) δ: 167.4 (C, O-*C*=O), 136.2 (C), 133.3 (CH), 130.4 (CH), 130.0 (CH), 129.1 (CH), 127.8 (CH), 123.2 (C), 121.4 (CH_2, CH_2CH=CH_2), 117.8 (C, *C*N), 82.0 (CH, Ar-C≡*C*-H), 81.8 (C, Ar-*C*≡C-H), 76.3 (C, CO_2CH_2C≡C-H), 76.0 (CH, CH_2C≡*C*-H), 53.9 (CH_2, CO_2CH_2C≡C-H), 50.7 (C), 40.7 (CH_2), 39.5 (CH_2, CH_2CH=CH_2).; LRMS m/z 278.10 (M^+ + 1), calcd. for $C_{18}H_{15}NO_2$ 277.1103; Anal.



90dc

calcd. for $C_{18}H_{15}NO_2$ (277.1103): C, 77.96; H, 5.45; N, 5.05, Found C, 77.85; H, 5.41; N, 5.12%.

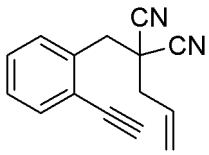
2-Cyano-2-(2-ethynyl-benzyl)-pent-4-enoic acid benzyl ester (90dc): Purified by column chromatography using EtOAc/hexane and isolated as a solid; IR (neat) ν_{max} 3288, 3069, 3032, 1744 (O-C=O), 1644, 1484, 1446, 1376, 1328, 1212, 1143, 1106, 1048, 993, 931, 759, 697, 637 and 612 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.50–7.47 (1H, m), 7.34–7.20 (8H, m) [Ar-*H*]; 5.84–5.74 (1H, m, CH_2CH=CH_2), 5.22–5.17 (4H, m, CH_2CH=CH_2, CO_2CH_2Ph), 3.50 (1H, d, *J* = 13.8 Hz), 3.39 (1H, d, *J* = 13.8 Hz), 3.27 (1H, s, Ar-C≡C-*H*), 2.83 (1H, dd, *J* = 13.8, 7.3 Hz, CH_2CH=CH_2), 2.55 (1H, dd, *J* = 13.8, 7.1 Hz, CH_2CH=CH_2); ^{13}C NMR ($CDCl_3$, DEPT–135) δ: 167.9 (C, O-*C*=O), 136.4 (C), 134.5 (C), 133.2 (CH), 130.5 (CH), 129.8 (CH), 129.0 (CH), 128.54 (2 x CH), 128.52 (CH), 128.3 (2 x CH), 127.7 (CH), 123.1 (C), 121.1 (CH_2, CH_2CH=CH_2), 118.1 (C, *C*N), 82.0 (CH, Ar-C≡*C*-H), 81.8 (C, Ar-*C*≡C-H), 68.2 (CH_2, CO_2CH_2Ph), 50.7 (C), 40.8 (CH_2), 39.6 (CH_2, CH_2CH=CH_2).; LRMS m/z 330.00 (M^+ + 1), calcd. for $C_{22}H_{19}NO_2$ 329.1416; Anal. calcd. for $C_{22}H_{19}NO_2$ (329.1416): C, 80.22; H, 5.81; N, 4.25, Found C, 80.15; H, 5.86; N, 4.33%.



90de

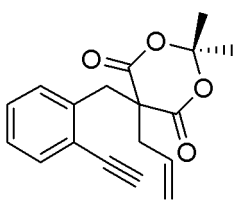
2-Cyano-2-(2-ethynyl-benzyl)-pent-4-enoic acid 2-isopropyl-5-methyl-cyclohexyl ester (90de): Purified by column chromatography using EtOAc/hexane and isolated as a gummy liquid; **$[\alpha]_D^{25}$ = 51.1 (*c* 0.1, $CHCl_3$);** IR (neat) ν_{max} 3296, 2957, 2871, 1735 (O-C=O), 1645, 1448, 1369, 1277, 1237, 1184, 1146, 1103, 1040, 989, 951, 763, 676 and 630 cm^{-1}; ^1H NMR ($CDCl_3$, 1:1 mixture of two diastereomers) δ 7.52 (2H, d, *J* = 7.6 Hz), 7.46 (2H, t, *J* = 7.6 Hz), 7.34–7.23 (4H, m) [Ar-*H*]; 5.87–5.76 (2H, m, 2 x CH_2CH=CH_2), 5.27–5.20 (4H, m, 2 x CH_2CH=CH_2), 4.73–4.66 (2H, m), 3.51–3.38 (4H, m), 3.32 (2H, s, 2 x Ar-C≡C-*H*), 2.87–2.79 (2H, m), 2.58–2.48 (2H, m), 1.94–1.82 (2H, m), 1.67–1.56 (6H, m), 1.45–1.39 (4H, m), 1.04–0.94 (4H, m), 0.90–0.79 (8H, m), 0.68 (3H, d, *J* = 7.2 Hz), 0.65 (3H, d, *J* = 7.2

Hz); ^{13}C NMR ($CDCl_3$, DEPT–135, 1:1 mixture of two diastereomers) δ 167.7 (C, O-*C*=O), 167.6 (C, O-*C*=O), 136.7 (C), 136.6 (C), 133.3 (CH), 133.2 (CH), 130.7 (CH), 130.5 (CH), 129.8 (CH), 129.6 (CH), 128.94 (CH), 128.92 (CH), 127.6 (CH), 127.5 (CH), 123.3 (C), 123.2 (C), 120.9 (2 x CH_2, 2 x $CH_2CH=CH_2$), 118.42 (C, *C*N), 118.37 (C, *C*N), 82.04 (CH, Ar-C≡*C*-H), 81.97 (CH, Ar-C≡*C*-H), 81.94 (C, Ar-*C*≡C-H), 81.89 (C, Ar-*C*≡C-H), 77.6 (CH), 77.4 (CH), 50.7 (C), 50.6 (C), 46.4 (CH), 46.3 (CH), 41.6 (CH_2), 40.8 (CH_2), 40.4 (CH_2), 40.1 (CH_2), 39.7 (CH_2), 39.2 (CH_2), 33.9 (2 x CH_2), 31.31 (CH), 31.27 (CH), 25.7 (2 x CH), 23.0 (CH_2), 22.9 (CH_2), 21.87 (CH_3), 21.83 (CH_3), 20.68 (CH_3), 20.66 (CH_3), 15.98 (CH_3), 15.73 (CH_3).; LRMS m/z 378.20 (M^+ + 1), calcd. for $C_{25}H_{31}NO_2$ 377.2355; Anal. calcd. for $C_{25}H_{31}NO_2$ (377.2355): C, 79.54; H, 8.28; N, 3.71, Found C, 79.45; H, 8.31; N, 3.77%.



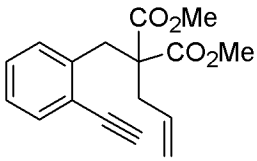
90df

2-Allyl-2-(2-ethynyl-benzyl)-malononitrile (90df): Purified by column chromatography using EtOAc/hexane and isolated as a liquid; IR (neat) ν_{max} 3292, 3272, 1484, 1445, 1286, 1098, 998, 940, 766, 697, 666 and 652 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 7.59 (1H, d, *J* = 7.6 Hz), 7.53 (1H, d, *J* = 7.6 Hz), 7.42 (1H, t, *J* = 7.6 Hz), 7.35 (1H, t, *J* = 7.6 Hz) [Ar-*H*]; 6.00–5.90 (1H, m, $CH_2CH=CH_2$), 5.45–5.40 (2H, m, $CH_2CH=CH_2$), 3.53 (2H, s, Ar-CH_2), 3.38 (1H, s, Ar-C≡C-*H*), 2.75 (2H, d, *J* = 7.2 Hz, $CH_2CH=CH_2$); ^{13}C NMR ($CDCl_3$, DEPT–135) δ: 134.2 (C), 133.5 (CH), 130.2 (CH), 129.4 (CH), 128.7 (CH), 128.6 (CH), 123.4 (C), 123.2 (CH_2, $CH_2CH=CH_2$), 114.8 (2 x C, 2 x *C*≡N), 82.8 (CH, Ar-C≡*C*-H), 81.6 (C, Ar-*C*≡C-H), 41.2 (CH_2), 39.9 (CH_2, $CH_2CH=CH_2$), 38.8 (C).; LRMS m/z 221.10 (M^+ + 1), calcd. for $C_{15}H_{12}N_2$ 220.1000; Anal. calcd. for $C_{15}H_{12}N_2$ (220.1000): C, 81.79; H, 5.49; N, 12.72, Found C, 81.72; H, 5.53; N, 12.85%.


90dg

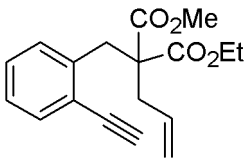
5-Allyl-5-(2-ethynyl-benzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione (90dg): Purified by column chromatography using EtOAc/hexane and isolated as a solid; IR (neat) ν_{max} 3732, 3270, 1776, 1742 (O-C=O), 1441, 1387, 1355, 1269, 1204, 1080, 1028,

950, 765 and 644 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.49 (1H, d, *J* = 7.6 Hz), 7.31–7.21 (3H, m) [Ar-*H*]; 5.74–5.64 (1H, m, CH_2CH=CH_2), 5.25 (1H, d, *J* = 17.2 Hz, CH_2CH=CH_2), 5.18 (1H, d, *J* = 10.0 Hz, CH_2CH=CH_2), 3.59 (2H, s, ArCH_2), 3.31 (1H, s, Ar-C≡C-*H*), 2.91 (2H, d, *J* = 7.6 Hz, CH_2CH=CH_2), 1.57 (3H, s, CH_3), 1.06 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 167.8 (2 x C, 2 x O-C=O), 136.8 (C), 133.5 (CH), 130.8 (CH), 130.6 (CH), 128.8 (CH), 127.6 (CH), 123.1 (C), 121.5 (CH_2, CH_2CH=CH_2), 105.6 (C, O-C-O), 81.9 (CH, Ar-C≡*C*-H), 81.2 (C, Ar-*C*≡C-H), 56.3 (C), 42.3 (2 x CH_2), 30.2 (CH_3), 28.4 (CH_3, CH_3).; LRMS m/z 297.0 (M-1), calcd. for $C_{18}H_{18}O_4$ 298.1205; Anal. calcd. for $C_{18}H_{18}O_4$ (298.1205): C, 72.47; H, 6.08, Found C, 72.41; H, 6.12%.



91dga

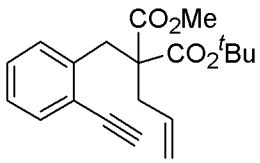
2-Allyl-2-(2-ethynyl-benzyl)-malonic acid dimethyl ester (91dga): Purified by column chromatography using EtOAc/hexane and isolated as a liquid; IR (neat) ν_{max} 3274, 3010, 2955, 1736 (O-C=O), 1731 (O-C=O), 1439, 1258, 1210, 1140, 1106, 1058, 760, 673, 634, 610 and 604 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.47 (1H, br d, *J* = 8.0 Hz), 7.26–7.22 (1H, m), 7.19–7.14 (2H, m) [Ar-*H*]; 5.92–5.85 (1H, m, CH_2CH=CH_2), 5.11–5.07 (2H, m, CH_2CH=CH_2), 3.69 (6H, s, 2 x CO_2CH_3), 3.53 (2H, s, ArCH_2), 3.25 (1H, s, Ar-C≡C-*H*), 2.62 (2H, d, *J* = 7.2 Hz, CH_2CH=CH_2); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 171.2 (2 x C, 2 x O-*C*=O), 138.7 (C), 133.23 (CH), 133.19 (CH), 129.9 (CH), 128.7 (CH), 126.9 (CH), 123.4 (C), 118.8 (CH_2, CH_2CH=CH_2), 82.4 (C, Ar-*C*≡C-H), 81.3 (CH, Ar-C≡*C*-H), 59.4 (C), 52.3 (2 x CH_3, 2 x CO_2CH_3), 37.5 (CH_2), 36.4 (CH_2, CH_2CH=CH_2).; LRMS m/z 287.00 (M^+ + 1), calcd. for $C_{17}H_{18}O_4$ 286.1205; Anal. calcd. for $C_{17}H_{18}O_4$ (286.1205): C, 71.31; H, 6.34, Found C, 71.25; H, 6.41%.



91dgb

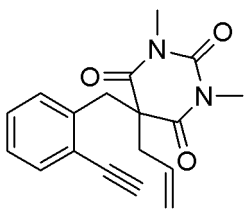
2-Allyl-2-(2-ethynyl-benzyl)-malonic acid ethyl ester methyl ester (91dgb): Purified by column chromatography using EtOAc/hexane and isolated as a liquid; IR (neat) ν_{max} 3278, 2984, 1736 (O-C=O), 1731 (O-C=O), 1441, 1273, 1210, 1141, 1106,

1047, 758 and 635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.48 (1H, d, *J* = 6.8 Hz), 7.28–7.18 (3H, m) [Ar-*H*]; 5.94–5.87 (1H, m, CH_2CH=CH_2), 5.13–5.08 (2H, m, CH_2CH=CH_2), 4.20–4.12 (2H, m, $CO_2CH_2CH_3$), 3.71 (3H, s, CO_2CH_3), 3.55 (2H, s, $ArCH_2$), 3.27 (1H, s, Ar-C≡C-*H*), 2.64 (2H, d, *J* = 7.2 Hz, CH_2CH=CH_2), 1.22 (3H, t, *J* = 7.2 Hz, $CO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 171.2 (C, O-*C*=O), 170.6 (C, O-*C*=O), 138.8 (C), 133.1 (2 x CH), 129.8 (CH), 128.6 (CH), 126.7 (CH), 123.3 (C), 118.6 (CH_2, CH_2CH=CH_2), 82.4 (C, Ar-*C*≡C-H), 81.2 (CH, Ar-C≡*C*-H), 61.3 (CH_2, $CO_2CH_2CH_3$), 59.2 (C), 52.2 (CH_3, CO_2CH_3), 37.4 (CH_2), 36.2 (CH_2, CH_2CH=CH_2), 13.9 (CH_3, $CO_2CH_2CH_3$).; LRMS m/z 301.00 (M^+ + 1), calcd. for $C_{18}H_{20}O_4$ 300.1362; Anal. calcd. for $C_{18}H_{20}O_4$ (300.1362): C, 71.98; H, 6.71, Found C, 71.85; H, 6.76%.



91dgi

2-Allyl-2-(2-ethynyl-benzyl)-malonic acid tert-butyl ester methyl ester (91dgi): Purified by column chromatography using EtOAc/hexane and isolated as a liquid; IR (neat) ν_{max} 3274, 2978, 1736 (O-C=O), 1731 (O-C=O), 1441, 1252, 1210, 1141, 1106, 1045, 922, 835, 763, 661 and 634 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.47 (1H, d, *J* = 7.6 Hz), 7.27–7.15 (3H, m) [Ar-*H*]; 5.95–5.85 (1H, m, CH_2CH=CH_2), 5.11–5.06 (2H, m, CH_2CH=CH_2), 3.70 (3H, s, CO_2CH_3), 3.51 (2H, s, $ArCH_2$), 3.26 (1H, s, Ar-C≡C-*H*), 2.59 (2H, d, *J* = 7.2 Hz, CH_2CH=CH_2), 1.40 (9H, s, O-C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 171.7 (C, O-*C*=O), 169.7 (C, O-*C*=O), 139.3 (C), 133.4 (CH), 133.2 (CH), 129.8 (CH), 128.6 (CH), 126.6 (CH), 123.4 (C), 118.5 (CH_2, CH_2CH=CH_2), 82.6 (C, Ar-*C*≡C-H), 81.9 (C, O-*C*(CH_3)$_3$), 81.3 (CH, Ar-C≡*C*-H), 59.5 (C), 52.1 (CH_3, CO_2CH_3), 37.6 (CH_2), 36.1 (CH_2, CH_2CH=CH_2), 27.8 (3 x CH_3, O-C(CH_3)$_3$).; LRMS m/z 329.00 (M+1), calcd. for $C_{20}H_{24}O_4$ 328.1675; Anal. calcd. for $C_{20}H_{24}O_4$ (328.1675): C, 73.15; H, 7.37, Found C, 73.22; H, 7.33%.

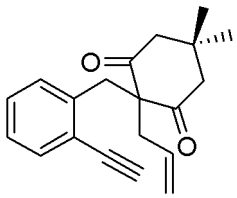


90da

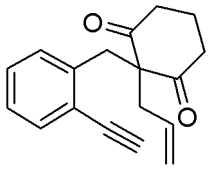
5-Allyl-5-(2-ethynyl-benzyl)-1,3-dimethyl-pyrimidine-2,4,6-trione (90da): Purified by column chromatography using EtOAc/hexane and isolated as a solid; IR (neat) ν_{max} 3261, 1691,

1688, 1678, 1444, 1380, 1323, 1289, 1085, 1046, 930, 761 and 637 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.45–7.43 (1H, dd, *J* = 6.9, 2.0 Hz,), 7.25–7.18 (2H, m), 7.01–6.99 (1H, m) [Ar-*H*]; 5.63–5.52 (1H, m, CH_2CH=CH_2), 5.16 (1H, d, *J* = 17.0 Hz, CH_2CH=CH_2), 5.06 (1H, d, *J* = 10.2 Hz, CH_2CH=CH_2), 3.46 (2H, s, $ArCH_2$), 3.27 (1H, s, Ar-C≡C-*H*), 3.12 (6H, s, 2 x NCH_3), 2.95 (2H, d, *J* = 7.2 Hz, CH_2CH=CH_2); ^{13}C NMR ($CDCl_3$, DEPT−135) δ 170.0 (2 x C, 2 x N-C=O), 150.5 (C, C=O), 136.7 (C), 133.2 (CH), 131.4 (CH), 129.4 (CH), 128.5 (CH), 127.7 (CH), 122.4 (C), 120.4 (CH_2, CH_2CH=CH_2), 81.7 (CH, Ar-C≡C-H), 81.1 (C, Ar-C≡C-H), 57.7 (C), 44.0 (CH_2), 40.7 (CH_2, CH_2CH=CH_2), 28.4 (2 x CH_3, 2 x N-CH_3).; LRMS m/z 311.10 (M^+ + 1), calcd. for $C_{18}H_{18}N_2O_3$ 310.1317; Anal. calcd. for $C_{18}H_{18}N_2O_3$ (310.1317): C, 69.66; H, 5.85; N, 9.03, Found C, 69.55; H, 5.91; N, 9.12%.

2-Allyl-2-(2-ethynyl-benzyl)-5,5-dimethyl-cyclohexane-1,3-dione (90dj): Purified by column chromatography using EtOAc/hexane and isolated as a liquid; IR (neat) ν_{max} 3289, 2956, 1724 (C=O), 1692 (C=O), 1462, 1330, 1254, 1203, 928, 764 692, 663, 646 and 619 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.48 (1H, d, *J* = 8.0 Hz), 7.28–7.19 (2H, m), 7.03 (1H, d, *J* = 8.0 Hz) [Ar-*H*]; 5.59–5.50 (1H, m, CH_2CH=CH_2), 5.08 (1H, dd, *J* = 16.0, 2.0 Hz, CH_2CH=CH_2), 4.99 (1H, dd, *J* = 8.0, 2.0 Hz, CH_2CH=CH_2), 3.29 (1H, s, Ar-C≡C-*H*), 3.27 (2H, s, $ArCH_2$), 2.65 (2H, d, *J* = 8.0 Hz, CH_2CH=CH_2), 2.56 (2H, d, *J* = 16.0 Hz), 2.43 (2H, d, *J* = 16.0 Hz), 0.97 (3H, s, CH_3), 0.85 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT−135) δ 209.2 (2 x C, 2 x C=O), 137.8 (C), 133.4 (CH), 133.3 (CH), 130.7 (CH), 128.7 (CH), 127.3 (CH), 123.0 (C), 119.5 (CH_2, CH_2CH=CH_2), 82.2 (C, Ar-C≡C-H), 82.1 (CH, Ar-C≡C-H), 68.4 (C), 53.0 (2 x CH_2), 42.2 (CH_2), 36.9 (CH_2, CH_2CH=CH_2), 30.6 (CH_3), 30.5 (C), 27.2 (CH_3).; LRMS m/z 295.25 (M^+ + 1), calcd. for $C_{20}H_{22}O_2$ 294.1620; Anal. calcd. for $C_{20}H_{22}O_2$ (294.1620): C, 81.60; H, 7.53, Found C, 81.52; H, 7.58%.

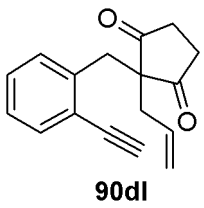


90dj



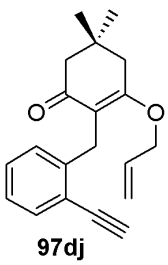
90dk

2-Allyl-2-(2-ethynyl-benzyl)-cyclohexane-1,3-dione (90dk): Purified by column chromatography using EtOAc/hexane and isolated as a solid; IR (neat) ν_{max} 3267, 2965, 1723 (C=O), 1692 (C=O), 1482, 1440, 1338, 1263, 1215, 1102, 1035, 1000, 927, 765, 676, 654 and 621 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.45 (1H, d, *J* = 7.6 Hz), 7.24 (1H, t, *J* = 7.6 Hz), 7.18 (1H, t, *J* = 7.6 Hz), 7.02 (1H, d, *J* = 7.6 Hz) [Ar-*H*]; 5.54–5.44 (1H, m, CH_2CH=CH_2), 5.02 (1H, *J* = 17.2 Hz, CH_2CH=CH_2), 4.99 (1H, *J* = 10.0 Hz, CH_2CH=CH_2), 3.31 (2H, s, ArCH_2), 3.30 (1H, s, Ar-C≡C-*H*), 2.67 (2H, d, *J* = 7.2 Hz, CH_2CH=CH_2), 2.49–2.34 (4H, m), 1.77–1.61 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 210.2 (2 x C, 2 x C=O), 138.3 (C), 133.3 (CH), 132.6 (CH), 130.2 (CH), 128.6 (CH), 126.9 (CH), 122.6 (C), 119.3 (CH_2, CH_2CH=*C*H_2), 81.9 (CH, Ar-C≡*C*-H), 81.8 (C, Ar-*C*≡C-H), 68.5 (C), 41.5 (CH_2), 40.28 (2 x CH_2), 40.20 (CH_2), 16.0 (CH_2).; LRMS m/z 267.10 (M + 1), calcd. for $C_{18}H_{18}O_2$ 266.1307; Anal. calcd. for $C_{18}H_{18}O_2$ (266.1307): C, 81.17; H, 6.81, Found C, 81.25; H, 6.77%.



90dl

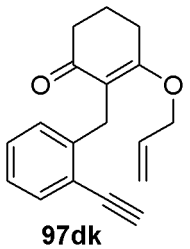
2-Allyl-2-(2-ethynyl-benzyl)-cyclopentane-1,3-dione (90dl): Purified by column chromatography using EtOAc/hexane and isolated as a solid; IR (neat) ν_{max} 3256, 1720 (C=O), 1644, 1482, 1412, 1337, 1279, 1181, 1099, 1028, 992, 921, 766, 711, 683, 636 and 612 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.46 (1H, d, *J* = 7.2 Hz), 7.33–7.17 (2H, m), 7.07 (1H, d, *J* = 7.6 Hz) [Ar-*H*]; 5.59–5.48 (1H, m, CH_2CH=CH_2), 5.06 (1H, *J* = 17.2 Hz, CH_2CH=CH_2), 5.02 (1H, *J* = 10.0 Hz, CH_2CH=CH_2), 3.31 (1H, s, Ar-C≡C-*H*), 3.20 (2H, s, ArCH_2), 2.53 (2H, d, *J* = 7.2 Hz, CH_2CH=CH_2), 2.49–2.37 (4H, m); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 215.7 (2 x C, 2 x C=O), 137.6 (C), 133.4 (CH), 131.5 (CH), 130.0 (CH), 128.7 (CH), 127.2 (CH), 122.7 (C), 120.0 (CH_2, CH_2CH=*C*H_2), 81.9 (CH, Ar-C≡*C*-H), 81.7 (C, Ar-*C*≡C-H), 61.8 (C), 39.4 (CH_2), 38.8 (CH_2), 36.4 (2 x CH_2).; LRMS m/z 253.10 (M + 1), calcd. for $C_{17}H_{16}O_2$ 252.1150; Anal. calcd. for $C_{17}H_{16}O_2$ (252.1150): C, 80.93; H, 6.39, Found C, 80.97; H, 6.44%.



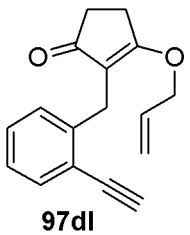
97dj

3-Allyloxy-2-(2-ethynyl-benzyl)-5,5-dimethyl-cyclohex-2-enone (97dj): Purified by column chromatography using EtOAc/ Hexane and isolated as a liquid; IR (neat) ν_{max} 3288, 2960, 2930, 1647, 1612, 1472, 1414, 1371, 1297, 1267, 1227, 1168, 1100, 1059, 928, 759, 662 and 638 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.42 (1H, d, *J* = 7.6 Hz, Ar-H), 7.17 (1H, t, *J* = 7.6 Hz, Ar-H), 7.06 (1H, t, *J* = 7.6 Hz, Ar-H), 7.00 (1H, d, *J* = 7.6 Hz, Ar-H), 5.81–5.71 (1H, m, OCH_2CH=CH_2), 5.14–5.09 (2H, m, OCH_2CH=CH_2), 4.48 (2H, d, *J* = 4.8 Hz, OCH_2CH=CH_2), 3.88 (2H, s, $ArCH_2$), 3.26 (1H, s, Ar-C≡C-*H*), 2.43 (2H, s), 2.30 (2H, s), 1.10 (6H, s, 2 x CH_3); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 197.7 (C, C=O), 170.6 (C, C-O), 143.9 (C), 132.8 (CH), 132.4 (CH), 128.5 (CH), 127.6 (CH), 125.1 (CH), 121.6 (C), 117.4 (C), 117.2 (CH_2, OCH_2CH=CH_2), 82.8 (C, Ar-*C*≡C-H), 80.8 (CH, Ar-C≡*C*-H), 68.0 (CH_2, OCH_2CH=CH_2), 50.2 (CH_2), 39.2 (CH_2), 32.2 (C), 28.5 (2 x CH_3), 26.1 (CH_2).; LRMS m/z 295.30 (M^+ +1), calcd. for $C_{20}H_{22}O_2$ 294.1620; Anal. calcd. for $C_{20}H_{22}O_2$ (294.1620): C, 81.60; H, 7.53, Found C, 81.71; H, 7.49%.

3-Allyloxy-2-(2-ethynyl-benzyl)-cyclohex-2-enone (97dk): Purified by column chromatography using EtOAc/ Hexane and isolated as a liquid; IR (neat) ν_{max} 3195, 2932, 1638, 1610, 1453, 1407, 1372, 1246, 1185, 1075, 1036, 937, 759, 726, 687, 654 and 615 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.42 (1H, d, *J* = 7.6 Hz, Ar-H), 7.17 (1H, t, *J* = 7.6 Hz, Ar-H), 7.07 (1H, t, *J* = 7.6 Hz, Ar-H), 7.01 (1H, d, *J* = 8.0 Hz, Ar-H), 5.82–5.72 (1H, m, OCH_2CH=CH_2), 5.16–5.11 (2H, m, OCH_2CH=CH_2), 4.49 (2H, br d, *J* = 4.8 Hz, OCH_2CH=CH_2), 3.88 (2H, s, $ArCH_2$), 3.26 (1H, s, Ar-C≡C-*H*), 2.58 (2H, t, *J* = 6.4 Hz), 2.42 (2H, t, *J* = 7.2 Hz), 2.06–1.99 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 197.9 (C, C=O), 172.4 (C, C-O), 143.8 (C), 132.7 (CH), 132.4 (CH), 128.5 (CH), 127.5 (CH), 125.1 (CH), 121.6 (C), 118.5 (C), 117.3 (CH_2, OCH_2CH=CH_2), 82.8 (C, Ar-*C*≡C-H), 80.9 (CH, Ar-C≡*C*-H), 68.1 (CH_2, OCH_2CH=CH_2), 36.3 (CH_2), 26.1 (CH_2),



97dk



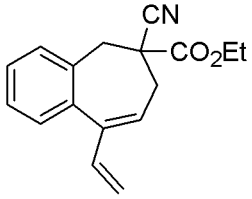
97dl

25.4 (CH_2), 20.9 (CH_2).; LRMS m/z 267.10 (M^+ +1), calcd. for $C_{18}H_{18}O_2$ 266.1307; Anal. calcd. for $C_{18}H_{18}O_2$ (266.1307): C, 81.17; H, 6.81, Found C, 81.10; H, 6.85%.

3-Allyloxy-2-(2-ethynyl-benzyl)-cyclopent-2-enone (97dl): Purified by column chromatography using EtOAc/ Hexane and isolated as a liquid; IR (neat) ν_{max} 3288, 2917, 1684, 1621, 1481, 1385, 1351, 1262,1228 1101, 1045, 966, 761, 670, 644 and 622 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.43 (1H, d, *J* = 7.2 Hz, Ar-H), 7.28–7.15 (2H, m, Ar-H), 7.10 (1H, t, *J* = 7.6 Hz, Ar-H), 5.91–5.82 (1H, m, $OCH_2C\mathit{H}=CH_2$), 5.25–5.20 (2H, m, $OCH_2CH=C\mathit{H}_2$), 4.61 (2H, d, *J* = 5.2 Hz, $OC\mathit{H}_2CH=CH_2$), 3.72 (2H, s, $ArC\mathit{H}_2$), 3.28 (1H, s, Ar-C≡C-*H*), 2.68 (2H, br t, *J* = 4.4 Hz), 2.50–2.48 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 204.2 (C, C=O), 184.7 (C), 142.0 (C), 132.5 (CH), 132.0 (CH), 128.6 (CH), 128.3 (CH), 125.6 (CH), 121.4 (C), 118.9 (C), 117.8 (CH_2, $OCH_2CH=\mathit{C}H_2$), 82.3 (C, Ar-*C*≡C-H), 81.3 (CH, Ar-C≡*C*-H), 69.6 (CH_2, $O\mathit{C}H_2CH=CH_2$), 33.4 (CH_2), 25.5 (CH_2), 24.9 (CH_2); LRMS m/z 253.50 (M^+ + 1), calcd. for $C_{17}H_{16}O_2$ 252.1150; Anal. calcd. for $C_{17}H_{16}O_2$ (252.1150): C, 80.93; H, 6.39, Found C, 80.85; H, 6.44%.

Experimental Procedure for the High-yielding Synthesis of Functionalized Carbocycles 8 and 9 via Enyne-RCM Reactions: A 10 mL oven-dried round bottom flask equipped with a magnetic stirring bar was charged with enyne **90** or **91** (0.1 mmol), CH_2Cl_2 (2 ml, 0.05 M) and first generation Grubbs' catalyst (4.11 mg, 0.005 mmol, 5 mol-%). The reaction mixture was stirred under N_2 at 40–45 °C for 4 to 24 h. Solvent CH_2Cl_2 were distilled off at ambient pressure and the enyne-RCM products **92** and **93** were purified by column chromatography (silica gel, mixture of hexane/ethyl acetate).

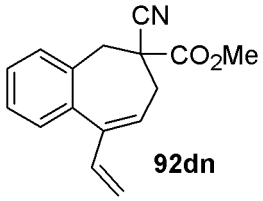
6-Cyano-9-vinyl-6,7-dihydro-5*H*-benzocycloheptene-6-carboxylic acid ethyl ester (92db): Purified by column chromatography using EtOAc/hexane and isolated as a liquid; IR (neat) ν_{max} 2981, 1743 (O-C=O), 1447, 1368, 1328, 1239, 1081, 1037, 917, 855 and 771 cm^{-1}; ^1H NMR



92db

($CDCl_3$) δ 7.38–7.28 (4H, m, Ar-*H*), 6.56 (1H, dd, *J* = 17.6, 10.8 Hz, C*H*=CH_2), 6.13 (1H, t, *J* = 7.2 Hz, olefinic-*H*), 5.27–5.20 (2H, m, CH=C*H*$_2$), 4.29 (2H, q, *J* = 7.2 Hz, $CO_2CH_2CH_3$), 3.22 (1H, d, *J* = 13.6 Hz), 3.03 (1H, d, *J* = 13.2 Hz), 2.55 (1H, dd, *J* = 13.2, 7.6 Hz), 2.33 (1H, dd, *J* = 13.6, 7.2 Hz), 1.35 (3H, t, *J* = 7.2 Hz, $CO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 167.9 (C, O-*C*=O), 143.8 (C), 136.9 (CH), 136.7 (C), 134.6 (C), 130.3 (CH), 128.9 (CH), 128.0 (CH), 127.5 (CH), 124.7 (CH), 119.7 (C, *C*N), 116.9 (CH_2, CH=*C*H_2), 62.9 (CH_2, $CO_2CH_2CH_3$), 54.7 (C), 39.2 (CH_2), 32.8 (CH_2), 14.0 (CH_3, $CO_2CH_2CH_3$).; LRMS m/z 268.50 (M^+ + 1), calcd. for $C_{17}H_{17}NO_2$ 267.1259; Anal. calcd. for $C_{17}H_{17}NO_2$ (267.1259): C, 76.38; H, 6.41; N, 5.24, Found C, 76.25; H, 6.48; N, 5.33%.

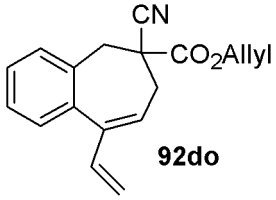
6-Cyano-9-vinyl-6,7-dihydro-5*H*-benzocycloheptene-6-carboxylic acid methyl ester



92dn

(92dn): Purified by column chromatography using EtOAc/hexane and isolated as a liquid; IR (neat) ν_{max} 2955, 2921, 2850, 1746 (O-C=O), 1444, 1245, 1091, 1040, 924, 854, 768, 699, 673, 652 and 627 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.38–7.30 (4H, m, Ar-*H*), 6.56 (1H, dd, *J* = 16.0, 12.0 Hz, C*H*=CH_2), 6.13 (1H, t, *J* = 7.6 Hz, olefinic-*H*), 5.25 (1H, d, *J* = 16.0 Hz, CH=C*H*$_2$), 5.21 (1H, d, *J* = 12.0 Hz, CH=C*H*$_2$), 3.85 (3H, s, CO_2CH_3), 3.22 (1H, d, *J* = 12.0 Hz), 3.03 (1H, d, *J* = 13.6 Hz), 2.56 (1H, dd, *J* = 13.6, 7.6 Hz), 2.34 (1H, dd, *J* = 13.6, 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 168.4 (C, O-*C*=O), 143.9 (C), 136.9 (CH), 136.7 (C), 134.5 (C), 130.3 (CH), 128.9 (CH), 128.0 (CH), 127.6 (CH), 124.5 (CH), 119.5 (C, *C*N), 117.0 (CH_2, CH=*C*H_2), 54.5 (C), 53.6 (CH_3, CO_2CH_3), 39.2 (CH_2), 32.8 (CH_2).; LRMS m/z 253.50 (M^+), calcd. for $C_{16}H_{15}NO_2$ 253.1103; Anal. calcd. for $C_{16}H_{15}NO_2$ (253.1103): C, 75.87; H, 5.97; N, 5.53, Found C, 75.71; H, 6.07; N, 5.61%.

6-Cyano-9-vinyl-6,7-dihydro-5H-benzocycloheptene-6-carboxylic acid allyl ester

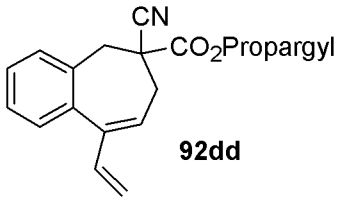


92do

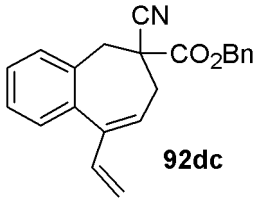
(92do): Purified by column chromatography using EtOAc/hexane and isolated as a liquid; IR (neat) ν_{max} 1745 (O-

C=O), 1448, 1226, 991, 920 and 769 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38–7.28 (4H, m, Ar-*H*), 6.56 (1H, dd, *J* = 17.6, 10.8 Hz, C*H*=CH_2), 6.13 (1H, t, *J* = 7.6 Hz, olefinic-*H*), 6.00–5.90 (1H, m, CO_2CH_2CH=CH_2), 5.40 (1H, dd, *J* = 18.8, 1.2 Hz, CH=CH_2), 5.32 (1H, dd, *J* = 10.4, 1.2 Hz, CH=CH_2), 5.24 (1H, d, *J* = 16.0 Hz, CO_2CH_2CH=CH_2), 5.21 (1H, d, *J* = 10.0 Hz, CO_2CH_2CH=CH_2), 4.72 (2H, dd, *J* = 5.6, 1.2 Hz, CO_2CH_2CH=CH_2), 3.23 (1H, d, *J* = 13.2 Hz), 3.04 (1H, d, *J* = 13.2 Hz), 2.56 (1H, dd, *J* = 13.6, 7.2 Hz), 2.35 (1H, dd, *J* = 13.6, 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 167.6 (C, O-*C*=O), 143.9 (C), 136.9 (CH), 136.7 (C), 134.5 (C), 130.8 (CH), 130.3 (CH), 128.9 (CH), 128.0 (CH), 127.6 (CH), 124.6 (CH), 119.6 (CH_2, CH=*C*H_2), 119.5 (C, *C*N), 117.0 (CH_2, CO_2CH_2CH=*C*H_2), 67.2 (CH_2, CO_2*C*H_2CH=CH_2), 54.7 (C), 39.3 (CH_2), 32.8 (CH_2).; LRMS m/z 280.00 (M^+ + 1), calcd. for $C_{18}H_{17}NO_2$ 279.1259; Anal. calcd. for $C_{18}H_{17}NO_2$ (279.1259): C, 77.40; H, 6.13; N, 5.01, Found C, 77.31; H, 6.18; N, 5.10%.

6-Cyano-9-vinyl-6,7-dihydro-5*H*-benzocycloheptene-6-carboxylic acid prop-2-ynyl ester (92dd): Purified by column chromatography using EtOAc/hexane and isolated as a liquid; IR (neat) ν_{max} 3290, 2923, 1750 (O-C=O), 1447, 1371, 1330, 1202, 1083, 1039, 923, 870, 805, 770, 671 and 659 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.39–7.28 (4H, m, Ar-*H*), 6.56 (1H, dd, *J* = 17.6, 10.8 Hz, C*H*=CH_2), 6.13 (1H, t, *J* = 7.6 Hz, olefinic-*H*), 5.26 (1H, d, *J* = 17.6 Hz, CH=CH_2), 5.22 (1H, d, *J* = 10.4 Hz, CH=CH_2), 4.82 (2H, dABq, *J* = 15.6, 2.4 Hz, CO_2CH_2C≡CH), 3.24 (1H, d, *J* = 13.6 Hz), 3.06 (1H, d, *J* = 13.6 Hz), 2.57 (1H, dd, *J* = 13.6, 7.2 Hz, CH_2CH=C), 2.56 (1H, t, *J* = 2.4 Hz, CO_2CH_2C≡C*H*), 2.36 (1H, dd, *J* = 13.6, 7.2 Hz, CH_2CH=C); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 167.2 (C, O-*C*=O), 144.1 (C), 136.89 (CH), 136.75 (C), 134.2 (C), 130.4 (CH), 128.9 (CH), 128.1 (CH), 127.7 (CH), 124.3 (CH), 119.1 (C, *C*N), 117.2 (CH_2, CH=*C*H_2), 77.2 (C, CO_2CH_2C≡CH), 76.1 (CH, CO_2CH_2C≡*C*H), 54.4 (C), 54.0 (CH_2), 39.2 (CH_2), 32.7 (CH_2).; LRMS m/z 277.30 (M^+), calcd. for $C_{18}H_{15}NO_2$



92dd

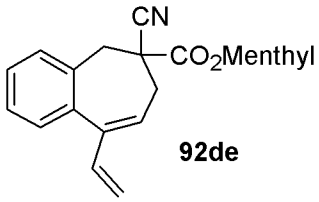


92dc

277.1103; Anal. calcd. for $C_{18}H_{15}NO_2$ (277.1103): C, 77.96; H, 5.45; N, 5.05, Found C, 77.85; H, 5.51; N, 5.15%.

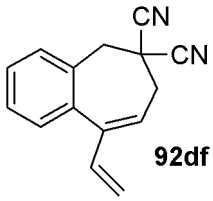
6-Cyano-9-vinyl-6,7-dihydro-5*H*-benzocycloheptene-6-carboxylic acid benzyl ester (92dc): Purified by column chromatography using EtOAc/hexane and isolated as a liquid; IR (neat) ν_{max} 3032, 1746 (O-C=O), 1448, 1214, 1079, 992, 915, 740, 697 and 644 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38–7.32 (7H, m), 7.27–7.22 (2H, m) [Ar-*H*]; 6.53 (1H, dd, *J* = 17.6, 10.8 Hz, C*H*=CH_2), 6.09 (1H, t, *J* = 7.6 Hz, olefinic-*H*), 5.29–5.19 (4H, m, CH=CH_2, CO_2CH_2Ph), 3.19 (1H, d, *J* = 13.6 Hz), 3.02 (1H, d, *J* = 13.6 Hz), 2.54 (1H, dd, *J* = 13.6, 7.6 Hz), 2.34 (1H, dd, *J* = 13.6, 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 167.6 (C, O-*C*=O), 143.9 (C), 136.9 (CH), 136.7 (C), 134.7 (C), 134.3 (C), 130.3 (CH), 128.9 (CH), 128.7 (2 x CH), 128.2 (2 x CH), 127.9 (2 x CH), 127.5 (CH), 124.5 (CH), 119.4 (C, *C*N), 117.0 (CH_2, CH=*C*H_2), 68.3 (CH_2, CO_2CH_2Ph), 54.6 (C), 39.2 (CH_2), 32.7 (CH_2).; LRMS m/z 330.55 (M^+ + 1), calcd. for $C_{22}H_{19}NO_2$ 329.1416; Anal. calcd. for $C_{22}H_{19}NO_2$ (329.1416): C, 80.22; H, 5.81; N, 4.25, Found C, 80.16; H, 5.87; N, 4.37%.

6-Cyano-9-vinyl-6,7-dihydro-5*H*-benzocycloheptene-6-carboxylic acid 2-isopropyl-5-methyl-cyclohexyl ester (92de): Purified by column chromatography using EtOAc/hexane and isolated as a gummy liquid; **$[\alpha]_D^{25}$ = 52.1° (*c* 0.1, $CHCl_3$);** IR (neat) ν_{max} 2957, 2870, 1736 (O-C=O), 1451, 1372, 1326, 1244, 1087, 1039, 987, 952, 911, 850, 769, 737 and 679 cm^{-1}; ^1H NMR ($CDCl_3$, 1:1.5 mixture of two diastereomers)□ δ 7.38–7.28 (8H, m, Ar-*H*), 6.56 (2H, dd, *J* = 17.6, 10.8 Hz, 2 x C*H*=CH_2), 6.12 (2H, t, *J* = 7.2 Hz, 2 x olefinic-*H*), 5.27–5.20 (4H, m, 2 x CH=CH_2), 4.76 (2H, dt, *J* = 10.8, 4.4 Hz), 3.21 (2H, t, *J* = 14.0 Hz), 3.02 (2H, dd, *J* = 13.2, 7.6 Hz), 2.59–2.50 (2H, m), 2.38–2.29 (2H, m), 2.05–1.99 (2H, m), 1.94–1.89 (2H, m), 1.75–1.70 (4H, m), 1.56–1.49 (4H, m), 1.12–1.03 (4H, m), 0.95–0.89 (8H, m), 0.79 (3H, d, *J* = 7.2 Hz), 0.76 (3H, d, *J* = 7.2 Hz) [2 x CH_3]; ^{13}C NMR ($CDCl_3$, DEPT–135,



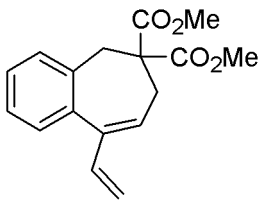
92de

1:1.5 mixture of two diastereomers) δ 167.46 (C, O-*C*=O), 167.43 (C, O-*C*=O), 143.9 (C), 143.7 (C), 136.97 (2 x CH), 136.78 (C), 136.75 (C), 134.71 (C), 134.6 (C), 130.4 (CH), 130.2 (CH), 128.9 (2 x CH), 127.96 (CH), 127.93 (CH), 127.53 (CH), 127.47 (CH), 124.9 (CH), 124.6 (CH), 119.74 (C, *C*N), 119.67 (C, *C*N), 116.9 (CH_2, CH=*C*H_2), 116.8 (CH_2, CH=*C*H_2), 77.33 (2 x CH), 54.9 (C), 54.8 (C), 46.87 (CH), 46.82 (CH), 40.4 (CH_2), 40.3 (CH_2), 39.4 (CH_2), 39.1 (CH_2), 34.1 (2 x CH_2), 33.0 (CH_2), 32.7 (CH_2), 31.4 (2 x CH), 26.2 (2 x CH), 23.17 (CH_2), 23.13 (CH_2), 21.93 (CH_3), 21.90 (CH_3), 20.79 (CH_3), 20.76 (CH_3), 16.01 (2 x CH_3).; LRMS m/z 378.00 (M^+ + 1), calcd. for $C_{25}H_{31}NO_2$ 377.2355; Anal. calcd. for $C_{25}H_{31}NO_2$ (377.2355): C, 79.54; H, 8.28; N, 3.71, Found C, 79.65; H, 8.22; N, 3.78%.



92df

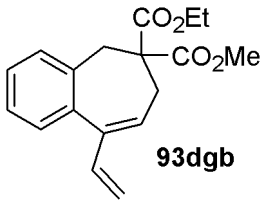
9-Vinyl-5,7-dihydro-benzocycloheptene-6,6-dicarbonitrile (92df): Purified by column chromatography using EtOAc/hexane and isolated as a liquid; IR (neat) ν_{max} 2252, 1648, 1470, 1440, 1303, 1074, 906, 776, 732, 686, 679 and 652 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.47–7.35 (4H, m, Ar-*H*), 6.59 (1H, dd, *J* = 17.6, 11.2 Hz, C*H*=CH_2), 6.13 (1H, t, *J* = 7.6 Hz, olefinic-*H*), 5.30 (2H, m, CH=C*H*$_2$), 3.21 (2H, s, Ar-C*H*$_2$), 2.53 (2H, d, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 146.1 (C), 136.7 (C), 136.3 (CH), 132.3 (C), 130.2 (CH), 129.3 (CH), 128.7 (CH), 128.6 (CH), 121.3 (CH), 118.7 (CH_2, CH=*C*H_2), 115.7 (2 x C, 2 x *C*≡N), 40.8 (C), 40.7 (CH_2), 34.6 (CH_2).; LRMS m/z 221.00 (M^+ + 1), calcd. for $C_{15}H_{12}N_2$ 220.1000; Anal. calcd. for $C_{15}H_{12}N_2$ (220.1000): C, 81.79; H, 5.49; N, 12.72, Found C, 81.65; H, 5.54; N, 12.66%.



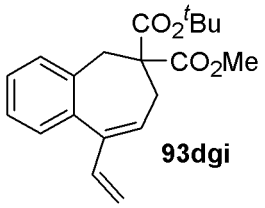
93dga

9-Vinyl-5,7-dihydro-benzocycloheptene-6,6-dicarboxylic acid dimethyl ester (93dga): Purified by column chromatography using EtOAc/hexane and isolated as a liquid; IR (neat) ν_{max} 2954, 1736 (O-C=O), 1732 (O-C=O), 1440, 1274, 1217, 1074, 761 and 649 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.39 (1H, d, *J* = 7.2 Hz), 7.33–7.23 (3H, m) [Ar-*H*]; 6.54 (1H, dd, *J* = 17.6, 10.8 Hz, C*H*=CH_2), 6.19 (1H, t, *J* =

7.6 Hz, olefinic-*H*), 5.20 (1H, d, *J* = 17.2 Hz, CH=C*H*$_2$), 5.13 (1H, d, *J* = 10.8 Hz, CH=C*H*$_2$), 3.74 (6H, s, 2 x CO_2CH_3), 3.11 (2H, s, ArC*H*$_2$), 2.40 (2H, d, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 171.4 (2 x C, 2 x O-*C*=O), 142.2 (C), 137.5 (CH), 136.90 (C), 136.85 (C), 130.6 (CH), 128.5 (CH), 127.6 (CH), 127.3 (CH), 126.5 (CH), 115.6 (CH_2, CH=*C*H_2), 67.0 (C), 52.7 (2 x CH_3, 2 x CO_2CH_3), 37.4 (CH_2), 31.0 (CH_2).; LRMS m/z 287.00 (M^+ + 1), calcd. for $C_{17}H_{18}O_4$ 286.1205; Anal. calcd. for $C_{17}H_{18}O_4$ (286.1205): C, 71.31; H, 6.34, Found C, 71.42; H, 6.29%.



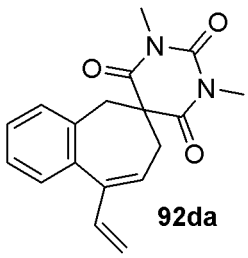
9-Vinyl-5,7-dihydro-benzocycloheptene-6,6-dicarboxylic acid ethyl ester methyl ester (93dgb): Purified by column chromatography using EtOAc/hexane and isolated as a liquid; IR (neat) ν_{max} 2981, 1736 (O-C=O), 1731 (O-C=O), 1449, 1254, 1214, 1073, 911, 856, 767, 697, 668 and 633 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.39 (1H, d, *J* = 7.2 Hz), 7.32–7.23 (3H, m) [Ar-*H*]; 6.52 (1H, dd, *J* = 17.6, 6.8 Hz, C*H*=CH_2), 6.17 (1H, t, *J* = 7.6 Hz, olefinic-*H*), 5.20 (1H, d, *J* = 17.6 Hz, CH=C*H*$_2$), 5.13 (1H, d, *J* = 11.2 Hz, CH=C*H*$_2$), 4.20 (1H, q, *J* = 7.2 Hz, $CO_2CH_2CH_3$), 4.19 (1H, q, *J* = 7.2 Hz, $CO_2CH_2CH_3$), 3.74 (3H, s, CO_2CH_3), 3.11 (2H, s, ArC*H*$_2$), 2.40 (2H, d, *J* = 7.2 Hz), 1.26 (3H, t, *J* = 7.2 Hz, $CO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 171.6 (C, O-*C*=O), 171.0 (C, O-*C*=O), 142.2 (C), 137.5 (CH), 137.0 (2 x C), 130.6 (CH), 128.6 (CH), 127.7 (CH), 127.3 (CH), 126.5 (CH), 115.6 (CH_2, CH=*C*H_2), 67.1 (C), 61.6 (CH_2, $CO_2CH_2CH_3$), 52.7 (CH_3, CO_2CH_3), 37.4 (CH_2), 31.1 (CH_2), 14.1 (CH_3, $CO_2CH_2CH_3$).; LRMS m/z 301.00 (M^+ + 1), calcd. for $C_{18}H_{20}O_4$ 300.1362; Anal. calcd. for $C_{18}H_{20}O_4$ (300.1362): C, 71.98; H, 6.71, Found C, 72.10; H, 6.67%.



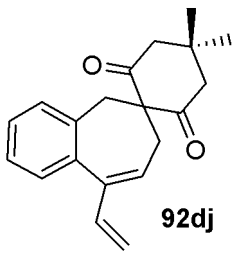
9-Vinyl-5,7-dihydro-benzocycloheptene-6,6-dicarboxylic acid tert-butyl ester methyl ester (93dgi): Purified by column chromatography using EtOAc/hexane and isolated as a liquid; IR (neat) ν_{max} 2978, 1735 (O-C=O), 1730 (O-C=O), 1443, 1368, 1277, 1254, 1222, 1155, 1074, 993, 911, 850, 770, 746, 683, 633 and 610 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.37 (1H, d, *J* = 7.2 Hz), 7.33–7.22 (3H, m) [Ar-*H*]; 6.54 (1H, dd, *J* =

17.6, 10.8 Hz, C*H*=CH_2), 6.18 (1H, t, *J* = 7.2 Hz, olefinic-*H*), 5.20 (1H, d, *J* = 17.6 Hz, CH=CH_2), 5.13 (1H, d, *J* = 10.8 Hz, CH=CH_2), 3.74 (3H, s, CO_2CH_3), 3.07 (2H, ABq, *J* = 16.0 Hz), 2.36 (2H, m), 1.45 (9H, s, 3 x CH_3); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 171.9 (C, O-*C*=O), 170.0 (C, O-*C*=O), 142.1 (C), 137.6 (CH), 137.2 (C), 137.0 (C), 130.6 (CH), 128.5 (CH), 127.9 (CH), 127.2 (CH), 126.4 (CH), 115.4 (CH_2, CH=*C*H_2), 81.9 (C), 67.8 (C), 52.4 (CH_3, CO_2CH_3), 37.4 (CH_2), 31.1 (CH_2), 27.9 (3 x CH_3).; LRMS m/z 329.00 (M^+ + 1), calcd. for $C_{20}H_{24}O_4$ 328.1675; Anal. calcd. for $C_{20}H_{24}O_4$ (328.1675): C, 73.15; H, 7.37, Found C, 73.25; H, 7.32%.

9-ethenyl-1',3'-dimethyl-5,7-dihydro-2'*H*-spiro[benzo[7]annulene-6,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione (92da): Purified by column chromatography using EtOAc/hexane and isolated as a liquid; IR (neat) ν_{max} 2928, 1686 (N-C=O), 1672, 1667, 1450, 1418, 1375, 1327, 1056, 779 and 624 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.34 (2H, d, *J* = 4.0 Hz), 7.28–7.24 (1H, m), 7.12 (1H, d, *J* = 7.6 Hz) [Ar-*H*]; 6.58 (1H, dd, *J* = 17.6, 10.8 Hz, C*H*=CH_2), 6.19 (1H, t, *J* = 7.6 Hz, olefinic-*H*), 5.22 (1H, d, *J* = 17.2 Hz, CH=CH_2), 5.16 (1H, d, *J* = 10.8 Hz, CH=CH_2), 3.32 (6H, s, 2 x NCH_3), 3.08 (2H, s, ArCH_2), 2.45 (2H, d, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 171.0 (2 x C, 2 x N-*C*=O), 151.3 (C, C=O), 141.7 (C), 137.5 (CH), 136.7 (C), 134.8 (C), 131.0 (CH), 128.8 (CH), 127.44 (CH), 127.32 (CH), 127.22 (CH), 115.8 (CH_2, CH=*C*H_2), 65.5 (C), 41.0 (CH_2), 31.9 (CH_2), 28.9 (2 x CH_3, 2 x NCH_3).; LRMS m/z 311.20 (M^+ + 1), calcd. for $C_{18}H_{18}N_2O_3$ 310.1317; Anal. calcd. for $C_{18}H_{18}N_2O_3$ (310.1317): C, 69.66; H,5.85; N, 9.03; Found C, 69.54; H, 5.90; N, 9.15%.

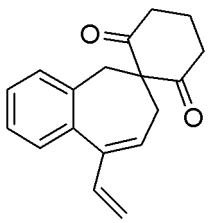


9-ethenyl-4',4'-dimethyl-5,7-dihydro-2'*H*,6'*H*-spiro[benzo[7]annulene-6,1'-cyclohexane]-2',6'-dione (92dj): Purified by column chromatography using EtOAc/hexane and isolated as a liquid; IR (neat) ν_{max} 2962, 2331, 1724 (C=O), 1691 (C=O), 1446, 1393, 1369, 1320, 1260, 1186, 1144, 1081, 990, 911, 806, 758, 670, 646



and 604 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.28–7.25 (2H, m), 7.23–7.17 (2H, m) [Ar-*H*]; 6.52 (1H, dd, *J* = 17.6, 10.8 Hz, C*H*=CH_2), 6.19 (1H, t, *J* = 7.6 Hz, olefinic-*H*), 5.16 (1H, d, *J* = 16.0 Hz, CH=C*H*$_2$), 5.11 (1H, d, *J* = 12.0 Hz, CH=C*H*$_2$), 2.99 (2H, s, ArCH_2), 2.80 (2H, d, *J* = 12.0 Hz), 2.57 (2H, d, *J* = 12.0 Hz), 2.29 (2H, d, *J* = 8.0 Hz), 1.10 (3H, s, CH_3), 0.92 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 206.9 (2 x C, 2 x C=O), 141.0 (C), 137.5 (CH), 137.0 (C), 135.9 (C), 130.2 (CH), 128.9 (CH), 128.7 (CH), 127.3 (CH), 126.8 (CH), 115.1 (CH_2, CH=*C*H_2), 80.0 (C), 51.3 (2 x CH_2), 38.5 (CH_2), 30.9 (C), 29.3 (CH_3), 28.9 (CH_2), 27.8 (CH_3).; LRMS m/z 295.00 (M^+ + 1), calcd. for $C_{20}H_{22}O_2$ 294.1620; Anal. calcd. for $C_{20}H_{22}O_2$ (294.1620): C, 81.60; H,7.53; Found C, 81.45; H, 7.48%.

9-ethenyl-5,7-dihydro-2'*H*,6'*H*-spiro[benzo[7]annulene-6,1'-cyclohexane]-2',6'-dione (92dk): Purified by column chromatography using EtOAc/hexane and isolated as a liquid; IR (neat) ν_{max} 2962, 1724 (C=O), 1692 (C=O), 1443, 1311, 1278, 1187, 1136, 1109, 1032, 993, 913, 768, 733 and 605 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30–7.25 (2H, m), 7.23–7.19 (2H, m) [Ar-*H*]; 6.52 (1H, dd, *J* = 17.6, 10.8 Hz, C*H*=CH_2), 6.16 (1H, t, *J* = 7.6 Hz, olefinic-*H*), 5.16 (1H, d, *J* = 17.6 Hz, CH=C*H*$_2$), 5.10 (1H, d, *J* = 11.2 Hz, CH=C*H*$_2$), 3.03 (2H, s, ArC*H*$_2$), 2.88–2.80 (2H, m), 2.73–2.66 (2H, m), 2.31 (2H, d, *J* = 7.2 Hz), 2.09–1.99 (1H, m), 1.90–1.79 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 206.8 (2 x C, 2 x C=O), 141.1 (C), 137.4 (CH), 136.9 (C), 135.9 (C), 130.1 (CH), 128.7 (2 x CH), 127.3 (CH), 126.8 (CH), 115.1 (CH_2, CH=*C*H_2), 81.4 (C), 38.2 (CH_2), 37.4 (2 x CH_2), 28.8 (CH_2), 18.3 (CH_2).; LRMS m/z 267.05 (M^+ + 1), calcd. for $C_{18}H_{18}O_2$ 266.1307; Anal. calcd. for $C_{18}H_{18}O_2$ (266.1307): C, 81.17; H, 6.81; Found C, 81.25; H, 6.76%.


92dk

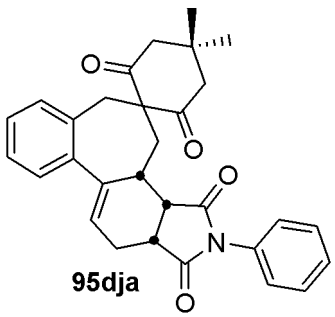
9-ethenyl-5,7-dihydro-2'*H*,5'*H*-spiro[benzo[7]annulene-6,1'-cyclopentane]-2',5'-dione (92dl): Purified by column chromatography using EtOAc/hexane and isolated as a solid; IR (neat) ν_{max} 2920, 1721 (C=O), 1446, 1420, 1277, 1157,


92dl

1031, 992, 912, 855, 770, 732 and 628 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.34–7.24 (3H, m), 7.15 (1H, d, *J* = 7.2 Hz) [Ar-*H*]; 6.58 (1H, dd, *J* = 17.6, 11.2 Hz, C*H*=CH_2), 6.10 (1H, t, *J* = 7.6 Hz, olefinic-*H*), 5.22 (1H, d, *J* = 17.6 Hz, CH=CH_2), 5.16 (1H, d, *J* = 10.8 Hz, CH=CH_2), 2.92–2.80 (4H, m), 2.78 (2H, s, ArCH_2), 2.10 (2H, d, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 213.1 (2 x C, 2 x C=O), 142.2 (C), 137.5 (CH), 136.6 (C), 134.7 (C), 130.6 (CH), 128.8 (CH), 127.5 (CH), 127.0 (CH), 126.2 (CH), 115. (CH_2, CH=*C*H_2), 69.9 (C), 36.6 (CH_2), 34.4 (2 x CH_2), 29.3 (CH_2); LRMS m/z 252.00 (M^+), calcd. for $C_{17}H_{16}O_2$ 252.1150; Anal. calcd. for $C_{17}H_{16}O_2$ (252.1150): C, 80.93; H, 6.39; Found C, 80.96; H, 6.34%.

Experimental Procedure for the Cascade Synthesis of Functionalized Carbocycles 11 and 12 via Enyne-RCM/Diels-Alder Reactions: A 10 mL oven-dried round bottom flask equipped with a magnetic stirring bar was charged with enyne **90** or **91** (0.1 mmol), CH_2Cl_2 (2 mL, 0.05 M) and first generation Grubbs' catalyst (4.11 mg, 0.005 mmol, 5 mol-%). The reaction mixture was stirred under N_2 at 40–45 °C for 4 to 24 h. Solvent CH_2Cl_2 was distilled off at ambient pressure and to the crude reaction mixture, *N*-phenylmaleimide **94a** (207.8 mg, 0.12 mmol, 1.2 equiv.) or diethyl acetylenedicarboxylate **94b** (0.12 mmol, 1.2 equiv.) and anhydrous toluene (2 mL) were added and heated at 110–120 °C under N_2 in a sealed glass tube for 13 to 21 h. Then toluene was removed and the residue was purified by column chromatography (silica gel, mixture of hexane/ethyl acetate) to give **95** and **96** respectively (see Table 16).

4',4'-Dimethyl-2-phenylspiro[1,2,3,3a,3b,4,5,6,12,12a-decahydrobenzo[3,4]cyclohepta[e]isoindole-5,1'-cyclohexane]-1,2',3,6'-tetraone

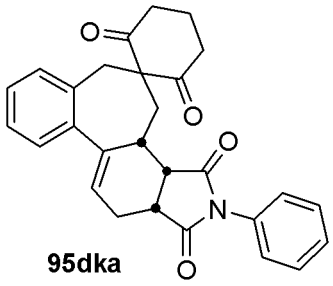


95dja

(95dja): Purified by column chromatography using EtOAc/hexane and isolated as a solid; IR (neat) ν_{max} 1698 (C=O), 1494, 1439, 1378, 1318, 1244, 1196, 1174, 1073, 915, 758, 734, 691, 672 and 630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.45 (2H, t, *J* = 7.6 Hz), 7.38 (1H, t, *J* = 7.6 Hz), 7.27–7.15

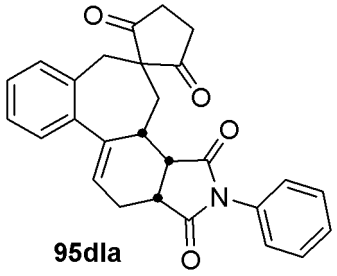
(5H, m), 6.98 (1H, dd, *J* = 7.2, 1.2 Hz) [Ar-*H*]; 6.04 (1H, m, olefinic-*H*), 3.34 (1H, t, *J* = 7.2 Hz), 3.24–3.16 (2H, m), 3.00–2.91 (2H, m), 2.82–2.75 (3H, m), 2.66–2.57 (2H, m), 2.48–2.33 (3H, m), 1.05 (3H, s, C*H*$_3$), 0.99 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 209.0 (C, C=O), 206.4 (C, C=O), 178.5 (C, N-C=O), 176.2 (C, N-C=O), 145.2 (C), 139.0 (C), 133.9 (C), 131.8 (C), 130.6 (CH), 129.0 (2 x CH), 128.5 (CH), 127.9 (CH), 127.6 (CH), 126.8 (CH), 126.2 (2 x CH), 125.0 (CH), 67.9 (C), 51.4 (CH_2), 50.9 (CH_2), 45.3 (CH), 40.8 (CH), 34.5 (CH_2), 33.7 (CH), 32.2 (CH_2), 30.8 (C), 28.9 (CH_3), 28.0 (CH_3), 25.2 (CH_2).; LRMS m/z 467.00 (M^+), calcd. for $C_{30}H_{29}NO_4$ 467.2097; Anal. calcd. for $C_{30}H_{29}NO_4$ (467.2097): C, 77.06; H, 6.25; N, 3.00; Found C, 77.14; H, 6.21; N, 3.10%.

2-Phenylspiro[1,2,3,3a,3b,4,5,6,12,12a-decahydrobenzo[3,4]cyclohepta[e]isoindole-5,1'-cyclohexane]-1,2',3,6'-tetraone (95dka): Purified by column chromatography using EtOAc/hexane and isolated as a liquid; IR (neat) ν_{max} 2297, 1705 (C=O), 1493, 1439, 1377, 1312, 1196, 1117, 832, 780, 690, 667, 653 and 621 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.48 (2H, t, *J* = 7.6 Hz), 7.36 (1H, t, *J* = 7.6 Hz), 7.30–7.18 (5H, m), 7.03 (1H, dd, *J* = 7.2, 1.6 Hz) [Ar-*H*]; 6.04 (1H, m, olefinic-*H*), 3.41–3.37 (1H, m), 3.28–3.19 (2H, m), 3.04–2.98 (2H, m), 2.93–2.70 (5H, m), 2.52–2.36 (3H, m), 2.09–1.87 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 209.0 (C, C=O), 206.4 (C, C=O), 178.5 (C, N-C=O), 176.2 (C, N-C=O), 145.2 (C), 139.0 (C), 133.9 (C), 131.8 (C), 130.7 (CH), 129.1 (2 x CH), 128.5 (CH), 127.9 (CH), 127.6 (CH), 126.9 (CH), 126.3 (2 x CH), 125.0 (CH), 69.3 (C), 45.4 (CH), 40.8 (CH), 37.7 (CH_2), 37.1 (CH_2), 34.2 (CH_2), 33.7 (CH), 32.1 (CH_2), 25.2 (CH_2), 18.3 (CH_2).; LRMS m/z 440.30 (M^+ + 1), calcd. for $C_{28}H_{25}NO_4$ 439.1784; Anal. calcd. for $C_{28}H_{25}NO_4$ (439.1784): C, 76.52; H, 5.73; N, 3.19; Found C, 76.44; H, 5.78; N, 3.25%.



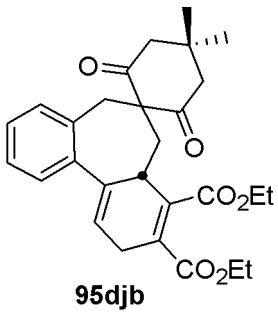
95dka

2-Phenylspiro[1,2,3,3a,3b,4,5,6,12,12a-decahydrobenzo[3,4]cyclohepta[e]isoindole-5,1'-cyclopentane]-1,2',3,5'-tetraone (95dla): Purified by column chromatography using EtOAc/hexane and isolated as a liquid; IR (neat) ν_{max} 3730, 1766, 1722 (C=O), 1701 (N-C=O), 1493, 1389, 1320, 1288, 1193, 1098, 1039, 828, 757, 695, 667 and 636 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.49–7.44 (2H, m), 7.41–7.37 (1H, m), 7.29–7.25 (2H, m), 7.20–7.17 (2H, m), 7.10–7.06 (2H, m) [Ar-*H*]; 6.12 (1H, m, olefinic-*H*), 3.43 (1H, br t, *J* = 7.6 Hz), 3.24–3.17 (2H, m), 3.07–3.01 (2H, m), 2.96–2.82 (4H, m), 2.54–2.45 (2H, m), 2.27 (1H, dd, *J* = 14.8, 12.0 Hz), 1.98 (1H, d, *J* = 14.8 Hz); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 215.9 (C, C=O), 212.6 (C, C=O), 178.5 (C, N-C=O), 176.1 (C, N-C=O), 145.1 (C), 139.0 (C), 132.4 (C), 131.7 (C), 130.3 (CH), 129.1 (2 x CH), 128.6 (CH), 128.15 (CH), 128.10 (CH), 127.3 (CH), 126.3 (2 x CH), 125.6 (CH), 57.6 (C), 45.2 (CH), 40.9 (CH), 34.8 (CH_2), 34.7 (CH_2), 34.2 (CH_2), 32.1 (CH), 31.0 (CH_2), 25.3 (CH_2).; LRMS m/z 426.30 (M^+ + 1), calcd. for $C_{27}H_{23}NO_4$ 425.1627; Anal calcd for $C_{27}H_{23}NO_4$ (425.1627): C, 76.22; H, 5.45; N, 3.29; Found C, 76.15; H, 5.49; N, 3.35%.



95dla

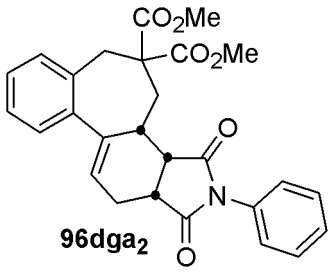
Diethyl 4,4-dimethyl-2,6-dioxospiro[cyclohexane-1,6'-(4a',5',6',7'-tetrahydro-2'*H*-dibenzo[a,c]cycloheptene)]-3',4'-dicarboxylate (95djb): Purified by column chromatography using EtOAc/hexane and isolated as a liquid; IR (neat) ν_{max} 2958, 1722 (C=O), 1694 (O-C=O), 1645, 1446, 1392, 1369, 1289, 1260, 1237, 1183, 1071, 1052, 1020, 732 and 632 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.22–7.16 (3H, m), 7.13–7.09 (1H, m) [Ar-*H*]; 5.74 (1H, dd, *J* = 4.8, 2.8 Hz, olefinic-*H*), 4.30–4.22 (4H, q, *J* = 7.2 Hz, 2 x $CO_2CH_2CH_3$), 3.70–3.64 (1H, m), 3.21–3.15 (4H, m), 2.82 (1H, d, *J* = 15.2 Hz), 2.71–2.57 (4H, m), 2.00 (1H, dd, *J* = 13.6, 12.0 Hz), 1.34 (3H, t, *J* = 7.2 Hz, $CO_2CH_2CH_3$), 1.29 (3H, t, *J* = 7.2 Hz, $CO_2CH_2CH_3$), 1.09 (3H, s, CH_3), 0.95 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 207.9 (C, C=O), 207.3 (C, C=O), 167.7 (C, O-C=O), 167.3 (C, O-C=O), 142.5 (C),



95djb

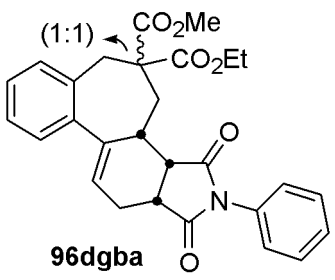
141.1 (C), 137.6 (C), 134.7 (C), 133.4 (C), 129.7 (CH), 128.0 (CH), 127.4 (CH), 127.2 (CH), 121.4 (CH), 66.8 (C), 61.19 (CH_2, $CO_2CH_2CH_3$), 61.17 (CH_2, $CO_2CH_2CH_3$), 52.1 (CH_2), 50.5 (CH_2), 41.1 (CH_2), 39.8 (CH_2), 36.6 (CH), 30.6 (C), 29.1 (CH_3), 28.4 (CH_2), 28.1 (CH_3), 13.96 (CH_3, $CO_2CH_2CH_3$), 13.94 (CH_3, $CO_2CH_2CH_3$).; LRMS m/z 463.00 (M^+ - 1), calcd. for $C_{28}H_{32}O_6$ 464.2199; Anal. calcd. for $C_{28}H_{32}O_6$ (464.2199): C, 72.39; H, 6.94; Found C, 72.61; H, 6.80%.

1,3-Dioxo-2-phenyl-2,3,3a,3b,4,6,12,12a-octahydro-1*H*-2-aza-benzo[3,4]cyclohepta[1,2-e]indene-5,5-dicarboxylic acid dimethyl ester (96dga$_2$):



96dga$_2$

Purified by column chromatography using EtOAc/hexane and isolated as a liquid; IR (neat) ν_{max} 2929, 1730 (O-C=O), 1701 (N-C=O), 1595, 1444, 1384, 1278, 1199, 1162, 1096, 1030, 943, 850, 822, 758, 690, 656, 631 and 608 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.44 (2H, t, *J* = 8.0 Hz), 7.36 (1H, t, *J* = 7.2 Hz), 7.26–7.18 (5H, m), 7.04 (1H, d, *J* = 4.8 Hz) [Ar-*H*]; 6.06 (1H, t, *J* = 3.2 Hz), 3.81 (3H, s, CO_2CH_3), 3.68 (3H, s, CO_2CH_3), 3.41–3.34 (3H, m), 3.02–2.92 (3H, m), 2.69 (1H, d, *J* = 15.2 Hz), 2.40–2.37 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 178.6 (C, O-C=O), 176.2 (C, O-C=O), 172.1 (C, N-C=O), 170.9 (C, N-C=O), 145.5 (C), 139.4 (C), 133.4 (C), 131.8 (C), 130.3 (CH), 129.0 (2 x CH), 128.4 (CH), 127.97 (CH), 127.9 (CH), 126.9 (CH), 126.2 (2 x CH), 125.1 (CH), 56.6 (C), 52.8 (CH_3, CO_2CH_3), 52.6 (CH_3, CO_2CH_3), 45.3 (CH), 40.7 (CH), 36.2 (CH_2), 34.5 (CH), 32.0 (CH_2), 25.3 (CH_2).; LRMS m/z 460.00 (M^+ + 1), calcd. for $C_{27}H_{25}NO_6$ 459.1682; Anal. calcd. for $C_{27}H_{25}NO_6$ (459.1682): C, 70.58; H, 5.48; N, 3.05; Found C, 70.49; H, 5.52; N, 3.10%.

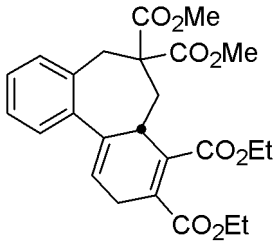


96dgba

1,3-Dioxo-2-phenyl-2,3,3a,3b,4,6,12,12a-octahydro-1H-2-aza-benzo[3,4]cyclohepta[1,2-e]indene-5,5-dicarboxylic acid ethyl ester methyl ester (96dgba):

Purified by column chromatography using EtOAc/hexane and isolated as a liquid; IR (neat) ν_{max} 2955, 1730 (O-C=O), 1710 (N-C=O), 1597, 1494, 1451, 1383, 1275, 1202, 1164, 1094, 1032, 944, 854, 755, 691, 656, 630 and 608 cm^{-1}; ^{1}H NMR ($CDCl_3$, 1:1 mixture of two diastereomers) δ 7.38–6.94 (18H, m) [Ar-*H*]; 5.98–5.96 (2H, br s, 2 x olefinic-*H*), 4.22–4.01 (4H, m, 2 x $CO_2CH_2CH_3$), 3.72 (3H, s, CO_2CH_3), 3.59 (3H, s, CO_2CH_3), 3.34–3.23 (6H, m), 2.95–2.84 (6H, m), 2.60 (2H, d, *J* = 12.0 Hz), 2.34–2.24 (4H, m), 1.23 (3H, t, *J* = 7.2 Hz, $CO_2CH_2CH_3$), 1.21 (3H, t, *J* = 7.2 Hz, $CO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$, DEPT–135, 1:1 mixture of two diastereomers) δ 178.7 (2 x C, 2 x O-C=O), 176.3 (2 x C, 2 x O-C=O), 172.4 (C, N-C=O), 171.7 (C, N-C=O), 171.0 (C, N-C=O), 170.5 (C, N-C=O), 145.6 (2 x C), 139.5 (2 x C), 133.6 (2 x C), 131.9 (2 x C), 130.47 (CH), 130.40 (CH), 129.1 (4 x CH), 128.6 (2 x CH), 128.1 (CH), 128.0 (CH), 127.9 (2 x CH), 127.0 (2 x CH), 126.4 (2 x CH), 126.3 (2 x CH), 125.1 (2 x CH), 61.8 (CH_2, $CO_2CH_2CH_3$), 61.6 (CH_2, $CO_2CH_2CH_3$), 56.7 (2 x C), 52.8 (CH_3, CO_2CH_3), 52.6 (CH_3, CO_2CH_3), 45.4 (2 x CH), 40.8 (2 x CH), 36.2 (2 x CH_2), 34.6 (2 x CH), 32.1 (2 x CH_2), 25.4 (2 x CH_2), 14.1 (CH_3, $CO_2CH_2CH_3$), 14.0 (CH_3, $CO_2CH_2CH_3$).; LRMS m/z 474.00 (M^+ + 1), calcd. for $C_{28}H_{27}NO_6$ 473.1838; Anal. calcd. for $C_{28}H_{27}NO_6$ (473.1838): C, 71.02; H, 5.75; N, 2.96; Found C, 71.12; H, 5.68; N, 3.07%.

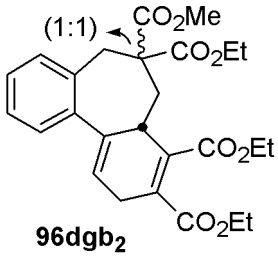
2,4a,5,7-Tetrahydro-dibenzo[a,c]cycloheptene-3,4,6,6-tetracarboxylic acid 3,4-diethyl ester 6,6-dimethyl ester (96dgab): Purified by column chromatography using EtOAc/hexane and isolated as a liquid; IR (neat) ν_{max} 2958, 1736 (O-C=O), 1730 (O-C=O), 1679, 1645, 1444, 1367, 1242, 1177, 1070, 932, 818, 757, 637 and 604 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.21–7.14 (3H, m), 7.11–7.08 (1H, m) [Ar-*H*]; 5.79 (1H, dd, *J* = 4.8, 2.4 Hz, olefinic-*H*), 4.34–4.24 (4H, m, 2 x $CO_2CH_2CH_3$), 3.74 (3H, s, CO_2CH_3), 3.61 (3H, s, CO_2CH_3), 3.55 (1H, m), 3.44–3.00 (4H, m), 2.88 (1H, br d, *J* = 13.2 Hz), 1.85 (1H, t, *J* = 12.8 Hz), 1.33 (6H, t, *J* = 7.2 Hz, 2 x $CO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$, DEPT–135) δ 172.0 (C, O-C=O), 169.6 (C, O-C=O), 167.4 (2 x C, 2 x O-C=O), 143.0 (C), 140.5 (C), 138.6 (C), 134.4 (C), 132.0 (C), 130.7



96dgab

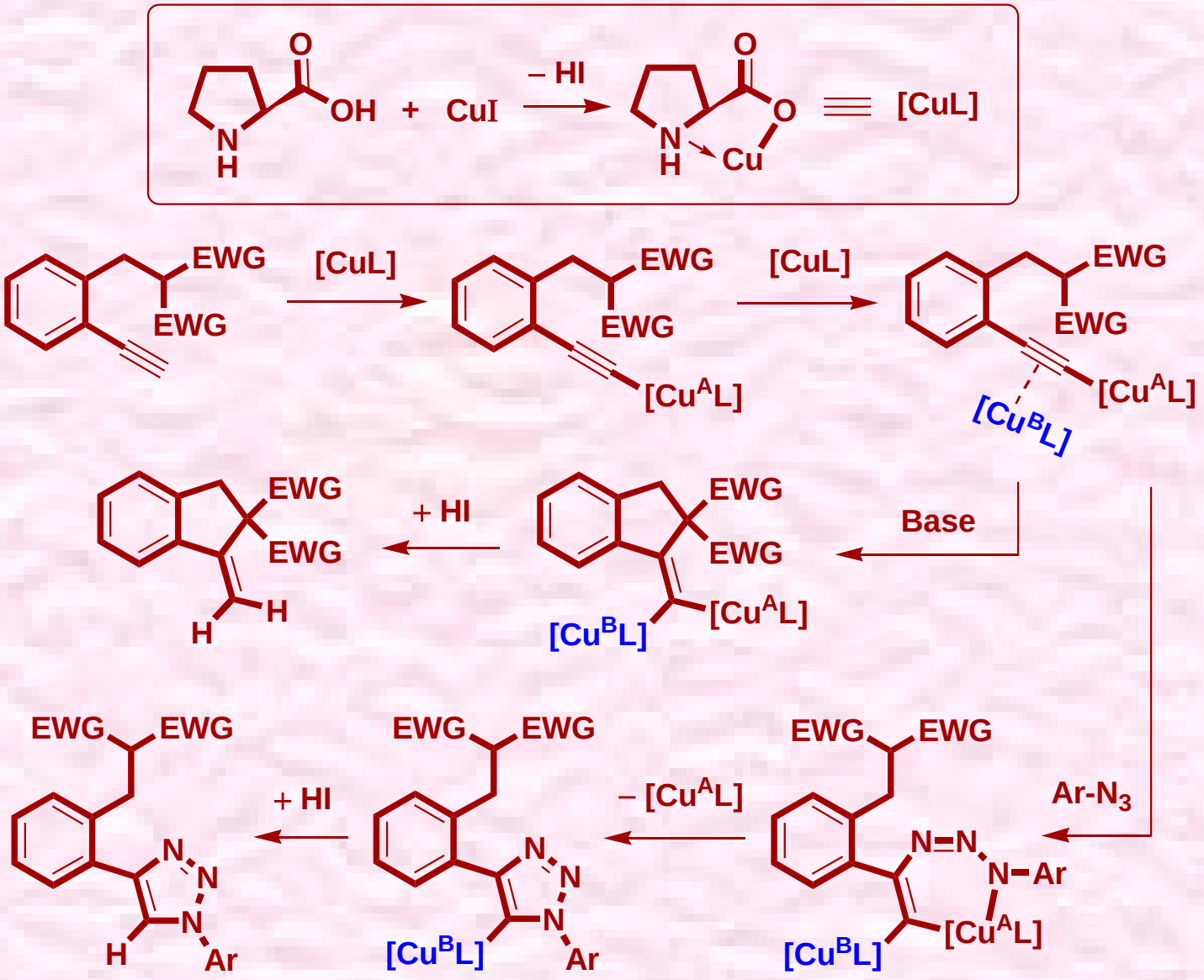
(CH), 127.8 (CH), 127.3 (CH), 127.2 (CH), 121.5 (CH), 61.24 (CH_2, $CO_2CH_2CH_3$), 61.18 (CH_2, $CO_2CH_2CH_3$), 56.0 (C), 52.9 (CH_3, CO_2CH_3), 52.0 (CH_3, CO_2CH_3), 41.0 (CH_2), 40.0 (CH_2), 37.2 (CH), 28.0 (CH_2), 13.9 (2 x CH_3, 2 x $CO_2CH_2CH_3$).; LRMS m/z 455.85 (M^+ - 1), calcd. for $C_{25}H_{28}O_8$ 456.1784; Anal. calcd. for $C_{25}H_{28}O_8$ (456.1784): C, 65.78; H, 6.18, Found C, 65.87; H, 6.13%.

2,4a,5,7-Tetrahydro-dibenzo[*a,c*]cycloheptene-3,4,6,6-tetracarboxylic acid 3,4,6-triethyl ester 6-methyl ester (96dgb$_2$): Purified by column chromatography using EtOAc/hexane and isolated as a liquid; IR (neat) ν_{max} 2983, 1736 (OC=O), 1728 (OC=O), 1644, 1445, 1368, 1241, 1180, 1099, 1069 and 758 cm^{-1}; ^1H NMR ($CDCl_3$, 1:1 mixture of two diastereomers) δ 7.19–7.14 (6H, m), 7.09–7.07 (2H, m) [Ar-*H*]; 5.79 (2H, m, olefinic-*H*), 4.33–4.23 (8H, m, 4 x $CO_2CH_2CH_3$), 4.20–4.17 (2H, m, $CO_2CH_2CH_3$), 4.04–4.02 (2H, m, $CO_2CH_2CH_3$), 3.73 (3H, s, CO_2CH_3), 3.59 (3H, s, CO_2CH_3), 3.58 (2H, m), 3.40–3.10 (8H, m), 2.86 (2H, m), 1.87 (2H, m), 1.32 (12H, t, *J* = 6.0 Hz, 4 x $CO_2CH_2CH_3$), 1.24 (3H, t, *J* = 6.0 Hz, $CO_2CH_2CH_3$), 1.13 (3H, t, *J* = 6.0 Hz, $CO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$, DEPT−135, 1:1 mixture of two diastereomers) δ 172.2 (C, O-C=O), 171.6 (C, O-C=O), 169.8 (C, O-C=O), 169.2 (C, O-C=O), 167.57 (C, O-C=O), 167.51 (C, O-C=O), 167.43 (C, O-C=O), 167.36 (C, O-C=O), 143.08 (C), 143.01 (C), 140.6 (2 x C), 138.9 (C), 138.7 (C), 134.54 (C), 134.45 (C), 132.0 (C), 131.8 (C), 131.0 (CH), 130.7 (CH), 127.8 (2 x CH), 127.36 (CH), 127.26 (CH), 127.2 (2 x CH), 121.5 (2 x CH), 61.8 (CH_2, $CO_2CH_2CH_3$), 61.29 (2 x CH_2, 2 x $CO_2CH_2CH_3$), 61.24 (2 x CH_2, 2 x $CO_2CH_2CH_3$), 61.1 (CH_2, $CO_2CH_2CH_3$), 56.1 (C), 55.9 (C), 52.8 (CH_3, CO_2CH_3), 52.0 (CH_3, CO_2CH_3), 41.0 (CH_2), 40.9 (CH_2), 40.0 (2 x CH_2), 37.3 (2 x CH), 28.03 (CH_2), 27.99 (CH_2), 14.0 (6 x CH_3, 6 x $CO_2CH_2CH_3$).; LRMS m/z 469.40 (M^+−1), calcd. for $C_{26}H_{30}O_8$ 470.1941; Anal. calcd. for $C_{26}H_{30}O_8$ (470.1941): C, 66.37; H, 6.43; Found C, 66.28; H, 6.47%.



96dgb$_2$

OBSERVATION OF DINUCLEAR ALKYNYL COPPER(I) COMPLEX IN CONIA-ENE AND HUISGEN CYCLOADDITION REACTIONS



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