Design and Development of Novel Synthetic Strategies towards Functionalized 3(2*H*)-Furanones

By

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TABLE OF CONTENTS

CHAPTER 1

3(2*H*)-Furanones: An Overview

CHAPTER 2

Tandem Reaction of 4-Halo-1,3-dicarbonyl Compounds with Alkynes towards 4-Vinyl-3(2*H*)-Furanones and Furanone fused 2-Pyridones

CHAPTER 3

Tandem *α*-Arylation/Cyclization of 4-Haloacetoacetates with Arynes: A Metal-Free Approach towards 4-Aryl-3-(2*H*)-Furanones

CHAPTER 4

Palladium Catalyzed Desymmetrization of Diazabicylic Olefins with 4-Halo-1,3-dicarbonyl compounds: Accessing 3(2*H*)-Furanone Appended Cyclopentenes

List of Abbreviations

Å	Angstrom
Ac	Acetyl
AcOH	Acetic acid
Ar	Argon
Ar-	Aryl
Bn	Benzyl
BoC	*tert*-Butyloxycarbonyl
Calcd	Calculated
CCDC	Cambridge crystallographic data centre
$CHCl_3$	Chloroform
°C	Degree celsius
DCE	Dichloroethane
DCM	Dichloromethane
d	Doublet
dd	Doublet of doublets
DMF	N, N-Dimethylformamide
DMSO	Dimethyl sulfoxide
DFT	Density functional theory
dr	Diastereomeric ratio
dt	Doublet of triplets
ee	Enantiomeric excess
equiv.	Equivalent
er	Enantiomeric ratio
ESI	Electron spray ionization

Et	Ethyl
Et_3N	Triethylamine
EtOAc	Ethyl acetate
EtOH	Ethanol
et al.	Et allii/alia
FT-IR	Fourier transform infrared spectroscopy
h	Hour
HRMS	High resolution mass spectrometry
Hz	Hertz
^{i}Pr	Isopropyl
$^{i}PrOH$	Isopropyl alcohol
J	Coupling constant
LUMO	Lowest unoccupied molecular orbital
m	Multiplet
m	Meta
MCR	Multicomponent reaction
Me	Methyl
MeOH	Methanol
mg	Milligram
MHz	Mega hertz
min	Minutes
mL	Millilitre
mmol	Millimolar
mol%	Mole percent
MP	Melting point
MS	Molecular sieves

MW	Microwave
NIS	N-iodosuccinimide
Na	Sodium
NMR	Nuclear magnetic resonance
o	Ortho
p	Para
Pd	Palladium
Ph	Phenyl
PTSA	*p*-Toluenesulfonic acid
q	Quartet
rt	Room temperature
Rh	Rhodium
Ru	Ruthenium
s	Singlet
t	Triplet
TBAI	Tetra-n-butylammonium iodide
tert	Tertiary
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMEDA	N,N,N′,N′-Tetramethylethylenediamine
TMS	Tetramethylsilane
Tol	Tolyl
Ts	Tosyl
H_2O	Water
δ	NMR chemical shift in parts per million

List of Tables

List of Figures

PREFACE

The formation of carbon-carbon and carbon-heteroatom bond constitute the primary aspect in organic synthesis. Developing new and efficient synthetic methodologies for the synthesis of new carbocycles and heterocycles with biological significance is always considered as a challenge to organic chemist. The development in the area of organic synthesis is always associated with the emergence of new methodologies with milder reaction conditions and greener output.

The structural diversity and broad spectra of biological applications of heterocycles makes them a group of continuously researched molecules. One such attractive moiety is 3(2*H*)-furanone, a five membered oxygen containing derivative of furan. The intriguing biological responses of this heterocycle makes this as an interesting synthetic target. The first report on the synthesis of 3(2*H*)-furanone derivatives appeared in 1958, after which several research groups worked and published methods for accessing this heterocycle. Initially, all efforts were centered on the total synthesis of 3(2*H*)-furanone containing natural products. In the past four decades, several new synthetic routes were reported for installing substituents at predetermined positions by starting from cleverly designed substrates. These methods involved the use of acids or bases as catalysts, organocatalysts, metal catalysts etc. Many tandem processes and successful enantioselective synthesis of complex natural products and other substituted 3(2*H*)-furanones were also established in literature. The mechanistic rationalizations of the reactions mentioned above, leave something to be desired, both from the theoretical and the experimental point of view. We believe that there is still large scope for developing new methods towards functionalized 3(2*H*)-furanones. Sustainable chemistry aspects are lacking in most of the reported preparative methods and validation of the reactions on a bulk scale is also missing. There are many 3(2*H*)-furanone containing natural products which have not been accessed by total synthesis. By using modern computational techniques new 3(2*H*)-furanone derivatives with specific biological properties could be designed and eventually be synthesized.

The whole thesis revolves around the utilization of 4-halo-1,3-dicarbonyl compounds as a precursor for the synthesis of 3(2*H*)-furanones and the chemistry involved includes the generation of an active methylene nucleophile from 4-halo-1,3-dicarbonyl compound which can be trapped by a electrophile and subsequent intramolecular cyclisation of the 4-halo-1,3-dicarbonyl part for the synthesis of the 4-substituted 3(2*H*)-furanones. Futher derivitastion is also possible by starting with appropriately functionalized 4-halo-1,3-dicarbonyl compounds

or electrophile. The thesis is organized into four chapters. **Chapter 1** initiates with a brief introduction on the development in the area of 3(2*H*)-furanones, especially with the review of literatutre on synthetic methodology developments. It also covers the biological applications of the synthesised library and biosynthesis as well.

In the remaining chapters we have tried to design and synthesize different substituted 3(2*H*)-furanones from 4-halo-1,3-dicarbonyl compounds, wherein we mainly foccused on developing protocols for trapping the carbanion generated from 4-halo-1,3-dicarbonyl compounds with various electrophiles such as alkynes, benzynes and diazabicyclic olefins.

Chaper 2 disusses about the reaction of 4-halo-1,3-dicarbonyl compounds with alkynes, where we have observed the formation of 4-vinyl-3(2*H*)-furanone formation along with its regioisomer, in contrary to our expectation of *E*/*Z* stereoisomers. The reaction proceeds *via* a tandem Michael addition and an intramolecular cyclization pathay. The formation of its regioisomer takes place *via* a stepwise [2+2] cycloaddition between enolate (of the 4-halo-1,3-dicarbonyl compound) and activated alkyne followed by a sequential 4π-ring opening and an intramolecular cyclization. Another interesting observation was the formation of 3(2*H*)-furanone fused 2-pyridone from the reaction of 4-bromo-3-oxo-*N*-alkyl (aryl)butanamide with activated alkynes.

Chapter 3 outlines the development of a mild and metal free approach towards the synthesis of 4-aryl-3(2*H*)-furanones from 4-halo-1,3-dicarbonyls and benzynes. The reaction proceeds *via* the nucleophilic addition of an active methylene compound to the aryne followed by ring closing of the adduct. Further derivatisation was done by synthesizing different heterocyclic analogues of aza-prostaglandins from 4-phenyl-3(2*H*)-furanones. The reaction pathway was further confirmed with a DFT calculation using M06L/SMD/6-311G(d,p) level density functional theory.

Transition metal catalyzed desymmetrization of diazabicyclic olefins *via* ring opening with active methylene nucleophiles generated from 4-halo-1,3-dicarbonyl compound was investigated in **Chapter 4**. Palladium catalyzed desymmetrization of diazabicyclic olefins *via* ring opening with nucleophile generated from 4-halo-1,3-dicarbonyl compound was also investigated. Desymmetrization of diazabicyclic olefins is an interesting and well explored area, while the reactivity of soft nucleophiles with the same is the least studied one. We have observed an interesting stereoselective synthesis of 3(2*H*)-furanones appended-1,3-*cis*-disubstituted cyclopentene from diazabicyclic olefin and 4-halo-1,3-dicarbonyls. The reaction

proceeds *via* the formation of a π-allylpalladium intermediate which is attacked by the active methylene species and an intramolecular nucleophilic substitution in the 4-halo1,3-dicarbonyl moiety. We could extend this methodology to cyclopropane-appended spirotricyclic olefins for synthesizing 3(2*H*)-furanone substituted spiro[2.4]hept-5-enes. We have also attempted an intramolecular Heck reaction for accessing a new class of 3(2*H*)-furanone fused tetrahydroazocine derivatives from an appropriately functionalized azaprostaglandin analogue.

Chapter 1

3(2*H*)-Furanones: An Overview

1.1. Introduction

Carbon–carbon and carbon–heteroatom bond-forming reactions constitute the backbone of synthetic organic chemistry. Chemists working on the same became contented when they replicated some of the most intriguing molecules of nature in laboratory. Many of these molecules have importance in drug discovery and have potential applications in many areas of science, technology, and everyday life. Among the different organic cores, oxygen containing heterocycles plays a significant role in organic, medicinal and material chemistry. Among these, furan is the most studied and explored core reported in literature. Even though literature is flooded with furan and related chemistry, there is still immense scope in establishing new libraries of furan derivatives from readily available precursors under mild reaction conditions.

An interesting derivative of furan reported in literature is furanone. They constitute an important class of five membered oxygen containing heterocycles, which forms the core structure of many naturally occurring motifs starting from the simple 2,5-dimethyl-4-hydroxy-3(2*H*)-furanone to complex natural products. The importance of furanones in the field of medicinal and pharmaceuticals are highly accomplished due to its attractive chemistry and biology. Depending on the structure, they can be classified into three main types: (i) 2(3*H*)-furanones **1**, (ii) 2(5*H*)-furanones **2**, and (iii) 3(2*H*)-furanones **3** (Figure 1.1).

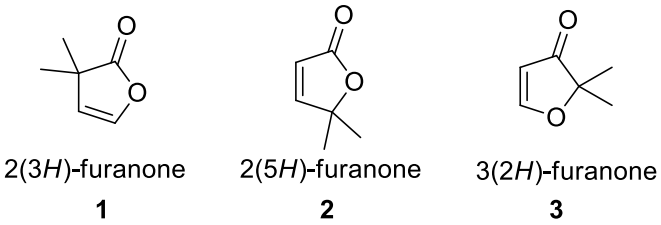


Figure 1.1: Different types of furanones.

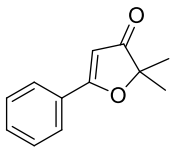
Furanones exhibit a broad range of therapeutic activities such as analgesic, anti-inflammatory, antibacterial, anticancer, anticonvulsant, antifungal, antimalarial, antimicrobial, antioxidant, antipsychotic, antituberculosis *etc*. As a result, they have got considerable attention as a synthetic bioactive target. Hence, the development of synthetic protocols and bioevaluation of the synthesized library is an active area of research.[1,2]

Biological properties exhibited by these furanones and their derivatives are versatile and as a result various synthetic methodologies are reported in literature regarding the synthesis and derivatization, such as acid, base or Lewis acid/base catalyzed, metal catalyzed, organocatalyzed, metal-free approaches, multicomponent reactions *etc*. The biological evaluation of the synthesized furanones showed marked improvements in the biological properties than the parent molecule (or natural product). Hence the development of new methodologies and utilization of developed methodologies for the derivatisation of furanones are still significant and valid. Since most of the syntheses and activity-based studies are reported on 2(5*H*)-furanones, we planned to develop synthetic routes towards functionalized 3(2*H*)-furanones. The reason for our interest in this area is discussed below.

1.2 Review of literature: 3(2*H*)-furanones

The story of 3(2*H*)-furanone started in the year 1954, when Brandt *et al.* isolated a 3(2*H*)-furanone moiety from the essential oil of *Myrtus bullata* (Banks and Solander), a shrub endemic to New Zealand and common in the lowland forests of the North Island (Fig 1.2). Initially the structure was wrongly assigned as 3-dihydro-3-methyl-6-phenyl-4-pyrone, however in 1958 Parker *et al*. reassigned the structure as 2,3-dihydro-2,2-dimethyl-3-oxo-5-phenylfuran, commonly called as bullatenone **4**.[3,4] In 1967, Lahey and MacLeod identified an anti-proliferative 3(2*H*)-furanone called geiparvarin **6** from the leaves of *Geijera parviflora* Lindl.[5] Later in 1970, Kupchan *et al.* isolated and characterized another 3(2*H*)-furanone containing macrocyclic diterpenoid named jatrophone **12** from *Jatropha gossyplifolia* L.[6,7]

Soon after, different natural products with 3(2*H*)-furanone core has been isolated and characterized, which includes nemoralisin A **7**, trachyspic acid **8**, pseurotin A **9**, eremantholide **10**, ciliarin **11,** hyperolactone C **13**, parvifloranine **14,** griseofulvin **15** *etc*. some of which are considered as promising pharmaceutical candidates (Figure 1.3).[2]



Bullatenone
4

Figure 1.2. The first reported source of bullatenone: *Myrtus bullata.*

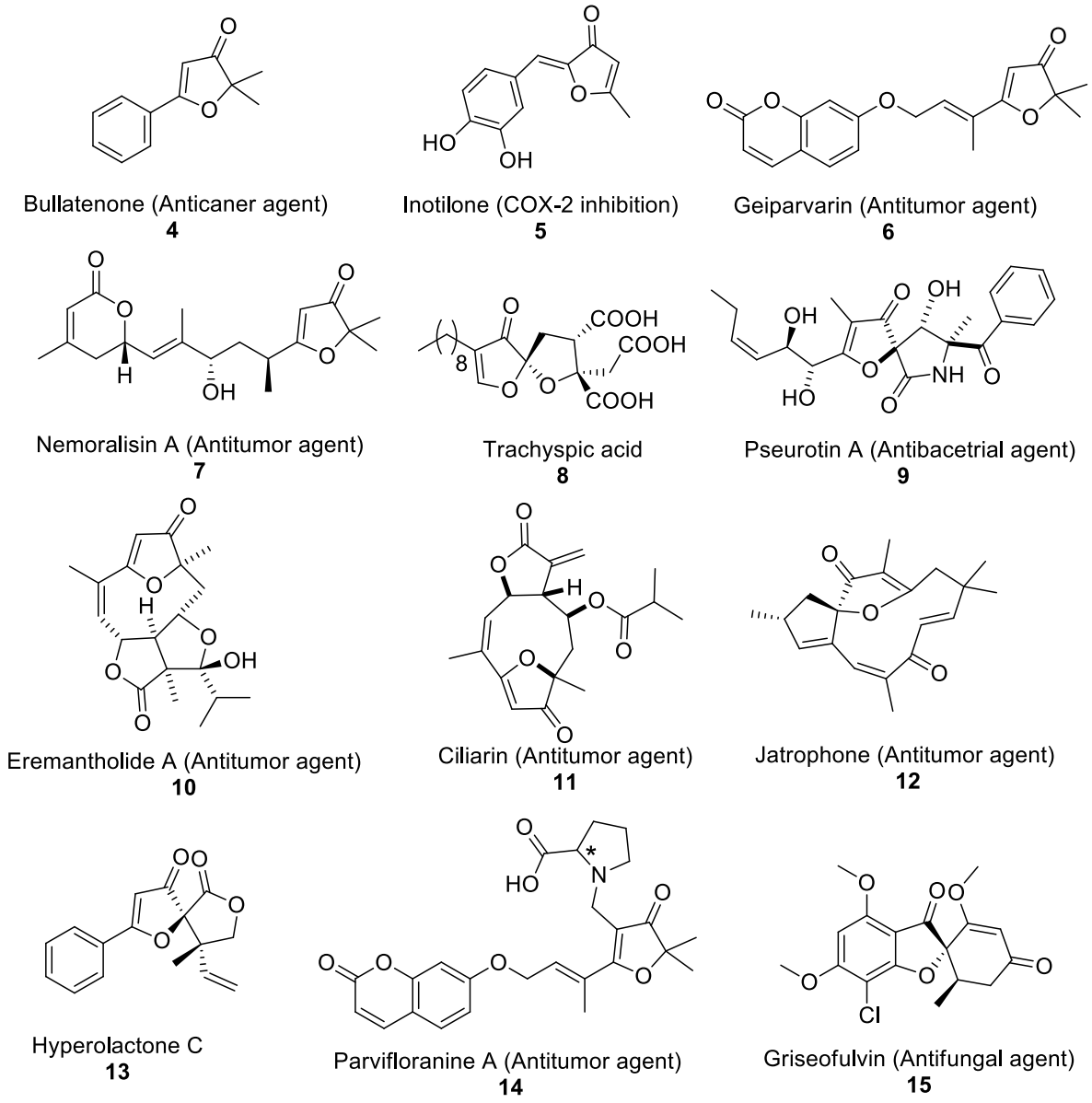


Figure 1.3: Natural products containing a 3(2*H*)-furanone core.

The intriguing biological activity of 3(2*H*)-furanone containing scaffolds can be attributed to the uniqueness of this oxygen containing heterocycle and also due to its ability to act as Michael acceptor. It has also been found that various substitutions on specified positions on the furanone moiety have marked improvements in its pharmacological effects.[2]

The development in the biological application of synthetic derivatives of furanones was ignited when Manfredini *et al*. reported the synthesis of a potent cytostatic compound **16** having a 3(2*H*)-furanone core with an IC_{50} value less than 0.3 mg/mL.[8] Encouraged by this result, a library of novel 5-(2-ethenylsubstituted)-3(2*H*)-furanone derivatives were synthesized and screened by Chimichi *et al*. in 2003 as an efficiant antiproliferative agent, and they ended up

with compounds **17** and **18** as potent *in vitro* antiproliferative agents against carcinoma, leukaemia, neuro blastoma and sarcoma cell lines as compared to the natural anticancer compound geiparvarin. The SAR studies revealed that the activity was mainly due to the presence of ethenyl moiety.[9] Mal *et al*. in 2014 reported the synthesis of furanone compounds **19-23** namely 2-methylsulfanyl-3(2*H*)-furanones and these derivatives were found to have anticancer, antibiotic, antiulcer and antiallergic activities.[10] Recently, in 2017 Irie *et al*. discovered a strong inhibitor of Cdc7, a 2,4,5-trisubstituted-3(2*H*)-furanone derivative **24** with an IC_{50} value of 0.6 nM in the presence of 1mM ATP. They reported that **24** induce apoptosis through selective inhibition of Cdc7 in cancer cells (Fig 1.4).[11]

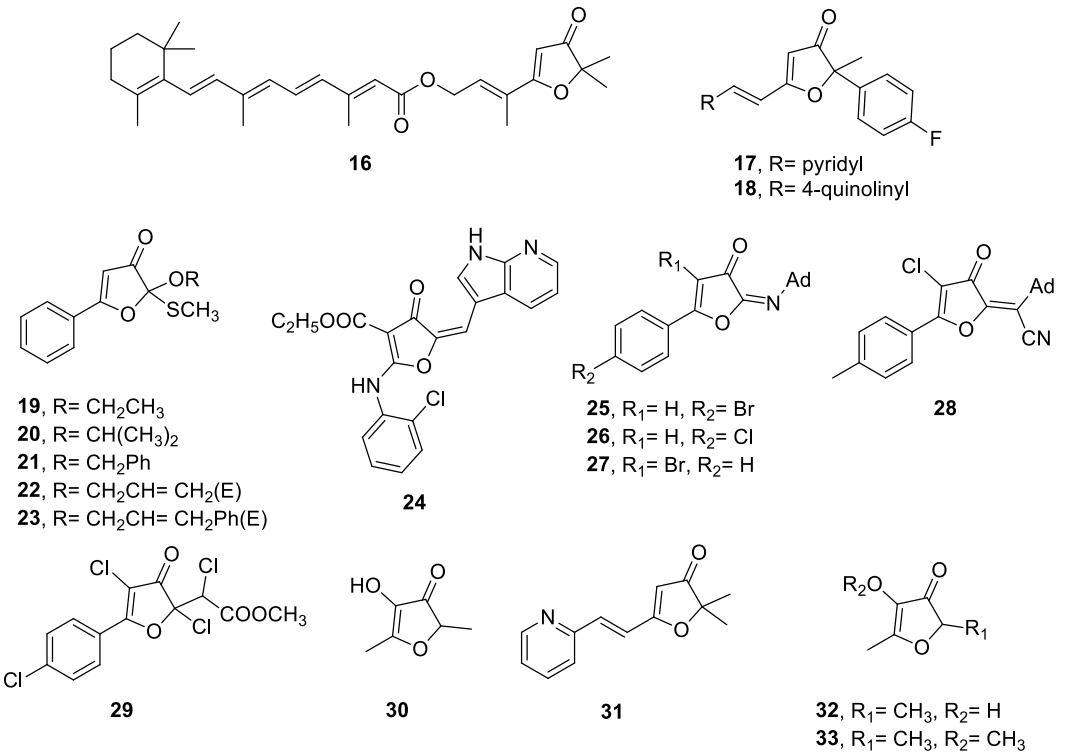


Figure 1.4. Pharmacologically active synthetic molecules containing a 3(2*H*)-furanone core.

Yanborisov and co-workers in 1989 synthesized powerful antibacterial agents namely, 2-[*N*-(11-adamantyl)imino]-4-*R*1-5-*p*-*R*-phenyl-2,3-dihydro-3-furanone derivatives **25-27** against *E. coli* with MIC of 31.0, 7.8 & 15.6 mg/mL, respectively.[12] Later in 1991, Kozminykh *et al.* prepared 5-aryl-2-acylmethylene-2,3-dihydro-3-furanone derivatives **28** and **29** with antimicrobial activity, against *E. coli* (MIC of 2.5 mg/mL) and against *S. aureus* (MIC of 15.6 mg/mL).[13] Sung *et al*. in 2007 reported the antimicrobial activity of 2,5-dimethyl-4-hydroxy-3(2*H*)-furanone (DMHF; compound **30**) against human pathogenic microorganisms including clinically isolated antibiotics-resistant strains.[2] In 1992 , Felman *et al*. demonstrated the synthesis and utilization of antiulcer agent 5-(2-ethenylsubstituted)-3(2*H*)-furanone and their

derivatives. Among the screened ones, compound **31** having a 2-pyridine moiety showed the best activity in the ethanol-necrosis model for duration of cytoprotection action. Its ability to protect gastric mucosa in acidified aspirin and indomethacin-induced lesion models at a dose of 10 mg/kg was also found to be equivalent to the parent drug, spizofurone (10 mg/kg).[14] In 2013 Schwab *et al*. reported the multiple therapeutic potentials of 4-hydroxy-2,5-dimethyl-3(2*H*)-furanone, **32** and the methoxy derivative **33**. They explored the potential nature of the compounds as antioxidative agents, inhibitors of onset of spontaneous cataracts, effective inhibitors of hyperpigmentation, as potent in DNA-breaking activity and for broad-spectrum antimicrobial activity in an energy dependent manner without hemolytic effect on human erythrocytes (Fig 1.4).[15]

Another important area other than pharmaceuticals where 3(2*H*)-furanones finds application is in food chemistry. 3(2*H*)-furanones namely furaneol or 4-hydroxy-2,5-dimethyl-3(2*H*)-furanone (HDMF), mesifuran (2,5-dimethyl-4-methoxy-3(2*H*)-furanone or DMMF), 4-Hydroxy-2 (or 5)-ethyl-5 (or 2) methyl-3(2*H*)-furanone (HEMF) and 4-hydroxy-5-methyl-3(2*H*)-furanone (HMF) (Fig 1.5) are aroma inducing agents found in variety of fruits such as pineapples, strawberries, blueberries, tomato, raspberry, kiwi, mango etc. and cooked foods like shoyu sauce, bread, beef etc.[16]

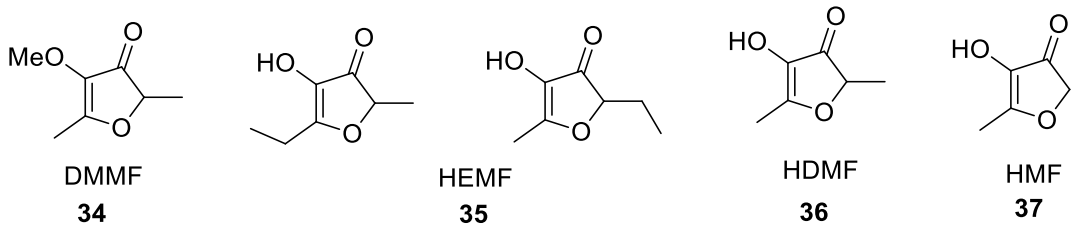


Figure 1.5. Different types of aroma inducing 3(2*H*)-furanones.

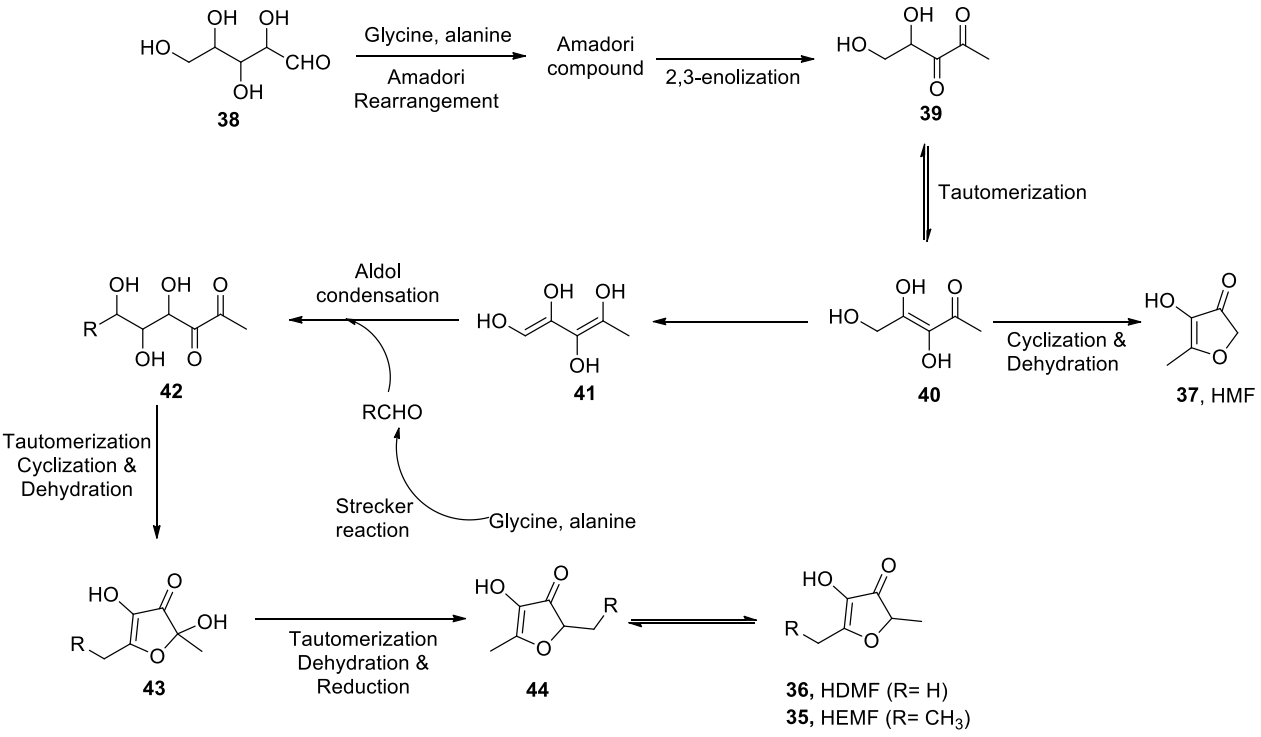
1.3 Biosynthesis of 3(2*H*)-furanones

Identification and isolation of 4-hydroxy-2 (or 5)-ethyl-5 (or 2) methyl-3(2*H*)-furanone (HEMF) **35** as a 3: 2 tautomeric mixture was first reported by Nunomuraa and coworkers in 1976.[17] It was first isolated from *shoyu*, a Japanese soy sauce. It has an intense sweet odor and the authors identified HEMF as one of the major flavor components in *shoyu*. They identified the different signals of the tautomers in the NMR spectra and hence calculated the tautomerism ratio based on proton intensities. They compared their spectral data with the same synthesized compounds from 3-heptyne-2,5-diol by Re and coworkers.[18] Thus, they elucidated the structure of aroma compound in *shoyu* as a 3(2*H*)-furanone. The homologues of HEMF **35** such as 4-

hydroxy-2,5-dimethyl-3(2*H*)-furanone (HDMF) **36** and 4-hydroxy-5-methyl-3(2*H*)-furanone (HMF) **37** have also been isolated from shoyu but the concentrations are much lower than that of HEMF.

In 1991, Sasaki and coworkers reported the biosynthesis of HEMF by yeasts. The authors suggested that HEMF was biosynthesized through the pentose-phosphate cycle such as D-xylulose 5-phosphate and the other homologue HDMF and HMF are produced from hexoses and pentoses respectively.[19,20]

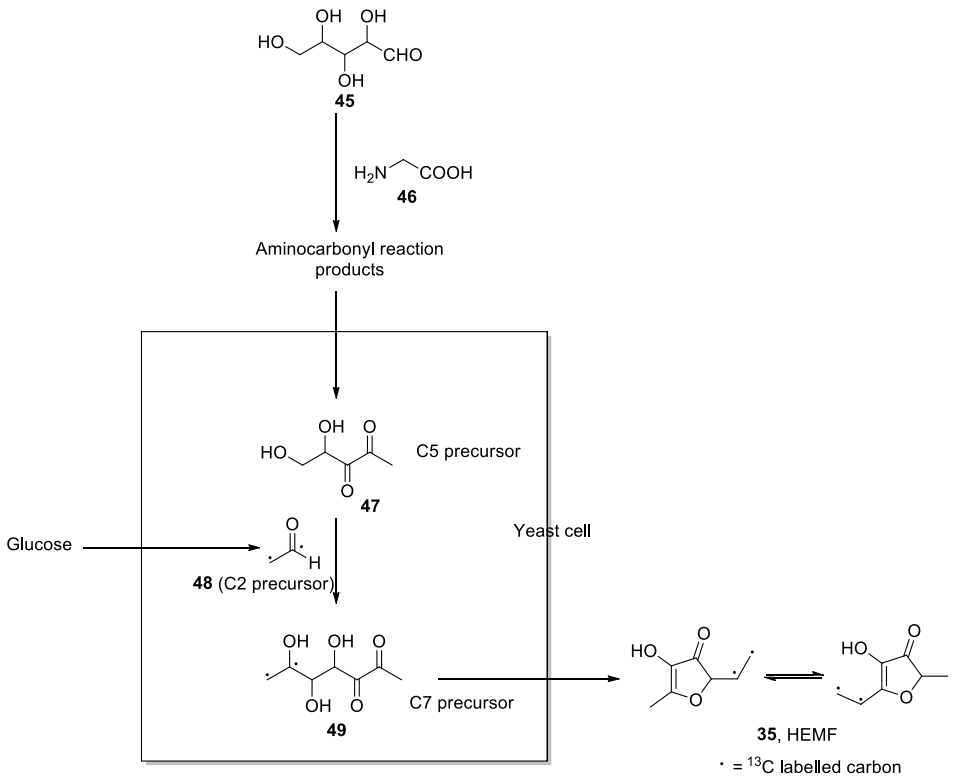
Later, Blank and coworkers reported that Maillard reaction of pentoses with the amino acids glycine and alanine as the main reason for the biosyntheses of HDMF and HEMF. Through their studies, the presence of HDMF and HEMF were identified in Maillard reaction systems based on pentoses and the amino acids glycine and alanine through GC-MS analysis. The formation of these furanones was further supported by reactions using ^{13}C-labeled amino acids. They also identified the role of Strecker aldehydes in furanone biosynthesis. They proposed the biosynthetic pathway as shown in scheme 1.1 It was initiated by the Amadori rearrangement of pentose sugar and alanine (or glycine) and subsequent decomposition *via* 2,3-enolization forming 1-deoxydiketose. This upon Strecker reaction followed by tautomerisation, cyclization and dehydration gave the 3(2*H*)-furanone HDMF and HEMF.[21]



Scheme 1.1

In 2003, Schwab and coworkers reported the biosynthesis of HDMF from D-fructose-1,6-bisphosphate by the yeast *Zygosaccharomyces rouxii*. They identified the intermediate of biosynthesis as α-dicarbonyl compound, which upon enzymatic reduction mediated by an oxidoreductase of the yeast cells gave HDMF. The same group extended their studies on pentose-phosphate and the biosynthesis of 3(2*H*)-furanones revealed that 4,5-dihydroxy-2,3-pentanedione was the key intermediate in HMF biosynthesis.[22,23]

Sugawara and coworkers analyzed the role of yeasts in the aminocarbonyl reaction for HEMF formation and found that it is not only provided a glucose metabolite but also combined the aminocarbonyl compound with the glucose metabolite. They found that HEMF formation was pretty good when yeast was cultivated in a medium where glycine concentration is high instead of alanine and also found that glucose concentration has also influence on the HEMF formation. Through their studies it was confirmed as the C5 precursor in the aminocarbonyl reaction of ribose and glycine and the C2 precursor as acetaldehyde by the glucose metabolism. They confirmed these results by ^{13}C labeling and spectral studies (scheme 1.2).[24]



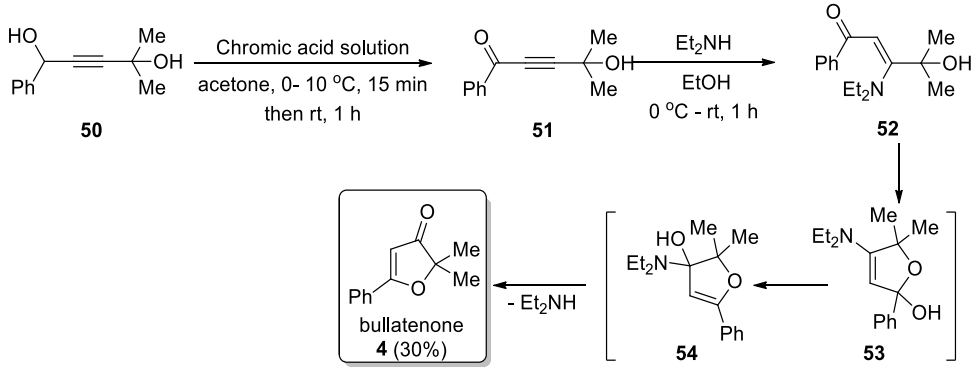
Scheme 1.2

1.4 Synthesis of 3(2*H*)-furanones

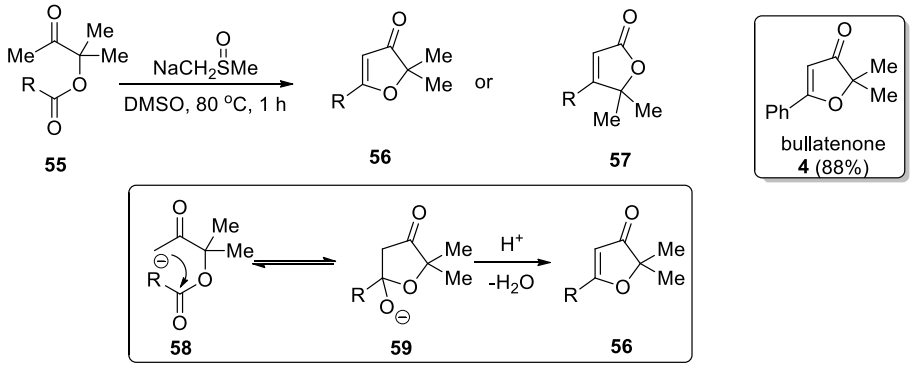
The methodologies reported for the synthesis of 3(2*H*)-furanone can be categorized based on the substitution patterns as (i) unsubstituted-3(2*H*)-furanones; (ii) 2-substituted-3(2*H*)-

furanones; (iii) 4-substituted-3(2*H*)-furanones; (iv) 5-substituted-3(2*H*)-furanones; (v) 2,4-disubstituted-3(2*H*)-furanones; (vi) 2,5-disubstituted-3(2*H*)-furanones; (vii) 4,5-disubstituted-3(2*H*)-furanones; (viii) 2,4,5-trisubstituted-3(2*H*)-furanones.

The first synthesis of 3(2*H*)-furanone was reported by Wilkinson *et al.* in 1958.[25] They confirmed the structure of the natural product bullatenone **4** by synthesizing it from 2-methylbut-3-yn-2-ol. The acetylenic diol **50** upon Jones oxidation followed by the addition of diethylamine to the acetylenic part and oxotropic rearrangement gave a dihydrofuran intermediate **54** from which diethylamine was eliminated to yield bullatenone in 30% yield (Scheme 1.3). In 1965, Lehmann reported a sodium dimsyl mediated reaction of *α*-acyloxy ketone in DMSO from which a mixture of *α*-hydroxyfuranone and butenolide was found to form, the latter in major proportion. Later, in 1981, Smith and co-workers studied the above-mentioned transformation in detail using *α*-acyloxy ketone **55** in such a way that 3(2*H*)-furanone was obtained as the sole product (Scheme 1.4).[26]



Scheme 1.3



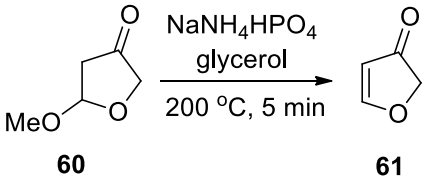
Scheme 1.4

Initially majority of the synthetic approaches were focussed on *α*'-hydroxy-1,3-diketones, *α*-acyloxy ketone and acetylenic alcohols as synthetic precursors. Later, different strategies

were reported with specific starting materials under discrete reaction conditions such as acid, base or Lewis acid/base catalyzed, metal catalyzed, organocatalyzed, metal free approaches, multicomponent reactions etc. Synthetic methodologies available for accessing 3(2*H*)-furanone core is discussed in the following sections.

1.4.1 Synthesis of unsubstituted-3(2*H*)-furanones

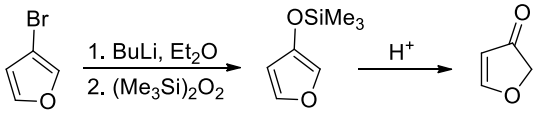
In 1981, Meister and Scharf reported the synthesis of unsubstituted 3(2*H*)-furanone **61** from 5-methoxy-3-oxo-tetrahydrofuran **60** (Scheme 1.5).[27] The reaction was effected by a base-catalyzed elimination of MeOH by pyrolysis in the presence of a sodium-ammonium-hydrogenphosphate ($NaNH_4HPO_4$) buffer.



60 **61**

Scheme 1.5

An easy access of unsubstituted 3(2*H*)-furanone was also reported by Taddei and co-workers in 1986 (Scheme 1.6).[28] The treatment of 3-bromofuran **62** with BuLi generated the corresponding heterocyclic anion which was trapped by bis-(trimethylsilyl) peroxide followed by protonolysis gave **61**.

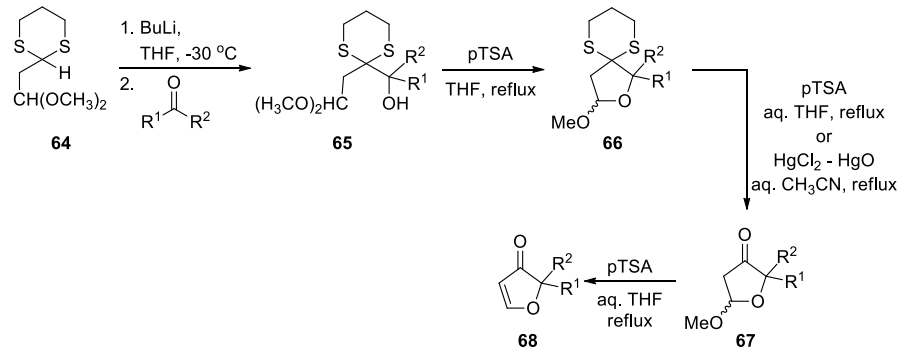


62 **63** **61**

Scheme 1.6

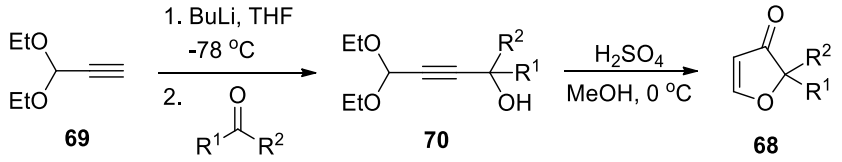
1.4.2 Synthesis of 2-substituted-3(2*H*)-furanones

An approach towards 2,2-disubstituted-3(2*H*)-furanone **68** starting from 2,2-dimethoxymethyl-1,3-dithiane **64** was published in 1973 by Sher *et al.* (Scheme 1.7).[29] The reaction proceeded *via* a nucleophilic addition, acid catalyzed intramolecular cyclisation and dehydration pathway.



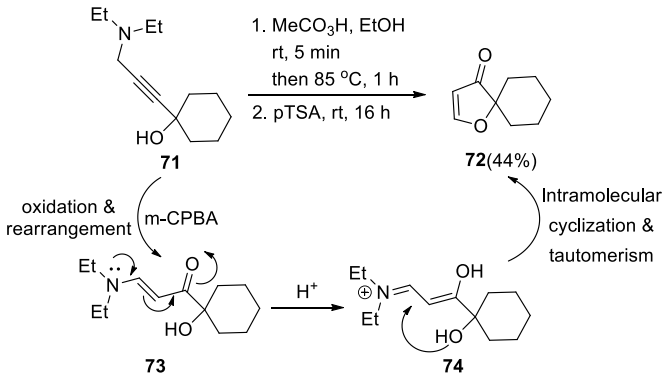
Scheme 1.7

Hiyama and co-workers reported another route for the synthesis of 2,2-disubstituted-3(2*H*)-furanones from propargylic alcohols (Scheme 1.8).[30] The addition of the lithiated propynal diethyl acetal **69** to different ketones furnished the corresponding 4-hydroxy-2-alkynyl diethyl acetals **70**. 2,2-disubstituted-3(2*H*)-furanones **68** was subsequently obtained by an acid (H_2SO_4) induced intramolecular cyclization of the propargylic alcohol.



Scheme 1.8

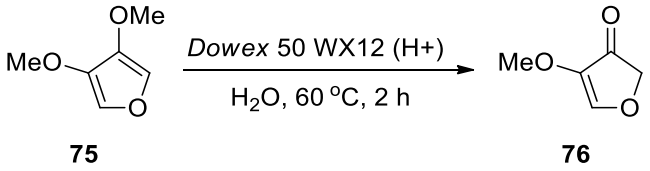
Inspired by the synthesis of 2,2-disubstituted-3(2*H*)-furanones from propargylic alcohols, Chen *et al.* reported an interesting improvement (Scheme 1.9).[31] They found that propargylamines could be converted to enaminones easily by oxidation with *m*-CPBA or peracetic acid. By combining this transformation and the above-mentioned intramolecular cyclization in one-pot, they demonstrated that *α*-hydroxylated propargylamine **71** could be converted to 2-spirocyclic-3(2*H*)-furanone **72**.



Scheme 1.9

1.4.3 Synthesis of 4-substituted-3(2*H*)-furanones

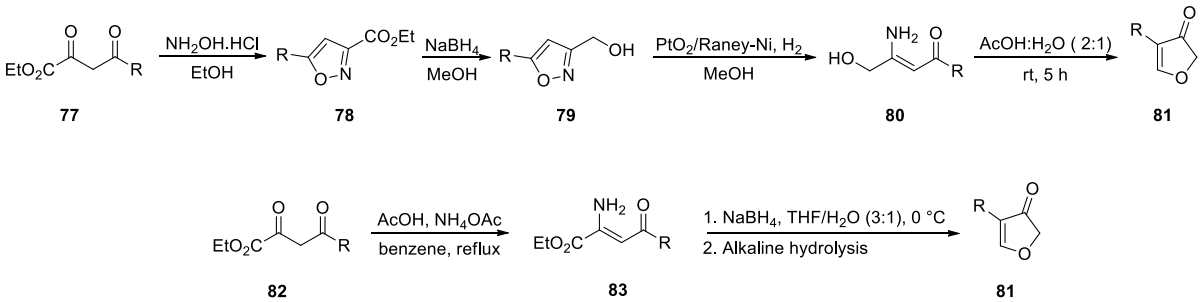
The synthesis of 4-methoxy-3(2*H*)-furanone **76** from 3,4-dimethoxyfuran **75** was reported in 1978 by Eugster *et al.* The hydrolysis of one methoxy-group in 3,4-dimethoxyfuran **75** by treatment with Dowex resin (acidic) in water at 60 ^{o}C furnished 4-methoxy-3(2*H*)-furanone **76** after 2 h (Scheme 1.10).[32]



75 **76**

Scheme 1.10

Simoni and co-workers later reported different strategies for the preparation of 4-substituted derivatives from ethyl 2,4-dioxoalkanoates (Scheme 1.11).[33] The reaction was initiated by the protection of *β*-diketones to 3,5-disubstituted isoxazoles **78** using hydroxylamine hydro-chloride. Then the ester functionality in **78** was converted into the corresponding primary alcohol **79** by reduction with sodium borohydride. This was followed by the hydrogenation of primary alcohol **79** with a PtO_2/Raney-Ni catalyst into *β*-enamino-ketone **80**. Finally, acid catalysed cyclodehydration of *β*-enamino-ketone **80** provided the corresponding 4-substituted-3(2*H*)-furanones **81**. The authors also showed that **81** could be accessed by another pathway without an isoxazole intermediate. Towards this end, 1,3-diketones were converted into the corresponding enaminones **83**.

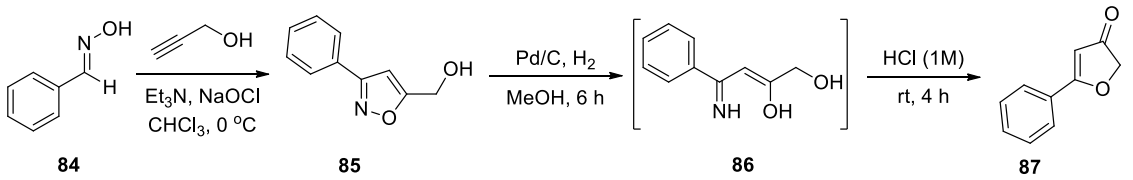


Scheme 1.11

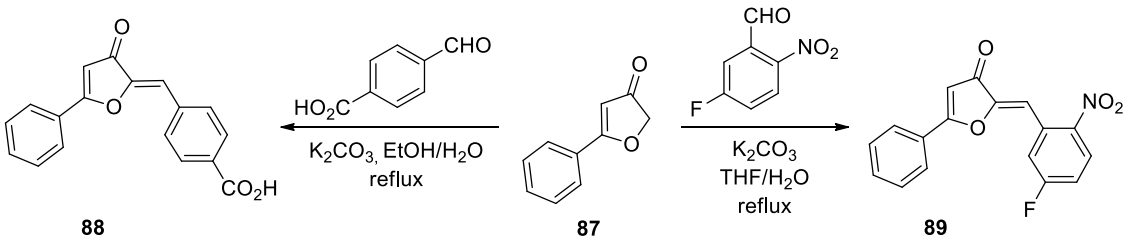
1.4.4 Synthesis of 5-substituted-3(2*H*)-furanones

Suliman and co-workers reported the synthesis of 5-substituted-3(2*H*)-furanone starting from benzaldehyde (Scheme 1.12).[34] The synthetic route involving three steps commenced with

the conversion of benzaldehyde to benzaldoxime **84** followed by 1,3-diploar cycloaddition with propargyl alcohol. Then the substituted isoxazole was subjected to catalytic hydrogenation with 10% Pd/C as catalyst and subsequent acidic hydrolysis furnished 5-phenyl-3(2*H*)-furanone **87** in 62% yield. The authors used the 5-substituted-3(2*H*)-furanone for the synthesis of two fluorescent organic dyes (Scheme 1.13). 5-phenyl-3(2*H*)-furanone **87** was subjected to aldol condensation with 5-fluoro-2-nitrobenzaldehyde and 4-formylbenzoic acid to afford the corresponding products **88** and **89**, respectively.

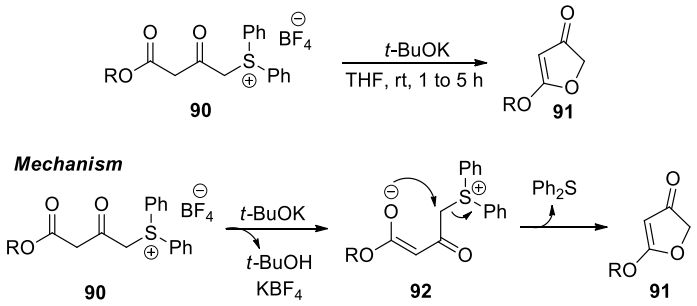


Scheme 1.12



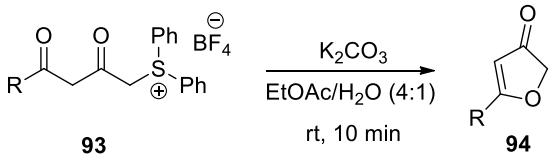
Scheme 1.13

In 2016, the group of Kawano described an intramolecular cyclization of 3-alkoxycarbonyl-2-oxopropyldiphenyl sulfonium **90** salts towards 5-substituted-3(2*H*)-furanones (Scheme 1.14).[35] Different sulfonium salts **90** were prepared by treating various substituted 4-bromo-acetoacetates with diphenylsulfide in the presence of $AgBF_4$. These sulfonium salts were then allowed to undergo intramolecular cyclization in the presence of a base which gave the corresponding 5-substituted-3(2*H*)-furanones **91.**



Scheme 1.14

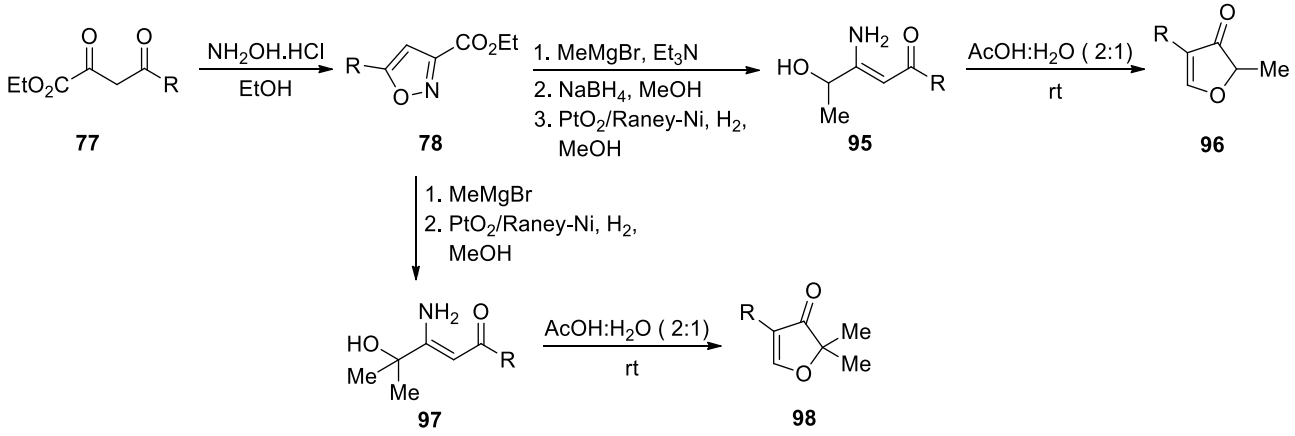
In 2018, the same authors reported the synthesis of 5-aryl-3(2*H*)-furanones by following a similar strategy as described above (Scheme 1.15). In this report they utilized (4-aryl-2,4-dioxobutyl) methyl-phenylsulfonium salts **93** instead of acetoacetates as in the previous case.[36] These sulfonium salts **93** upon base induced intramolecular cyclization afforded 5-aryl-3(2*H*)-furanone **94**.



Scheme 1.15

1.4.5 Synthesis of 2,4-disubstituted-3(2*H*)-furanones

Simoni and co-workers also utilized ethyl-2,4-dioxoalkanoates as starting materials for synthesizing 2,4-disubstituted 3(*2H*)-furanones (Scheme 1.16).[33]

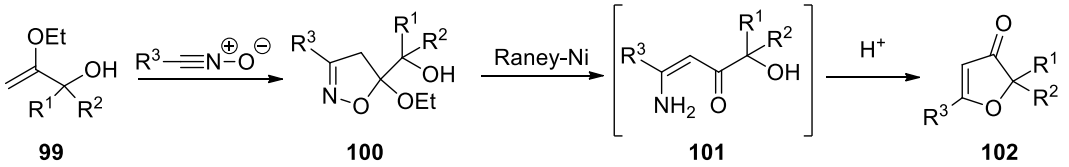


Scheme 1.16

As described earlier, the first step of the synthetic route involved the conversion of a *β*-diketone into 3,5-disubstituted isoxazoles **78**. Then the ester moiety of the isoxazoles was converted into a secondary or tertiary alcohol function by a two-stage protocol. Its first step consisted in the reaction of the isoxazole with methyl magnesium iodide, and the second step was either reduction using sodium borohydride for secondary alcohols or hydrogenation with a PtO_2/Raney-Ni mixture for tertiary alcohols. The reduction product of the secondary alcohol was then hydrogenated to the *β*-enamino-ketone **95**. The aminoketones **95** and **97** were further subjected to acid catalysed cyclodehydration to generate the corresponding 3(*2H*)-furanones **96** and **98**, respectively.

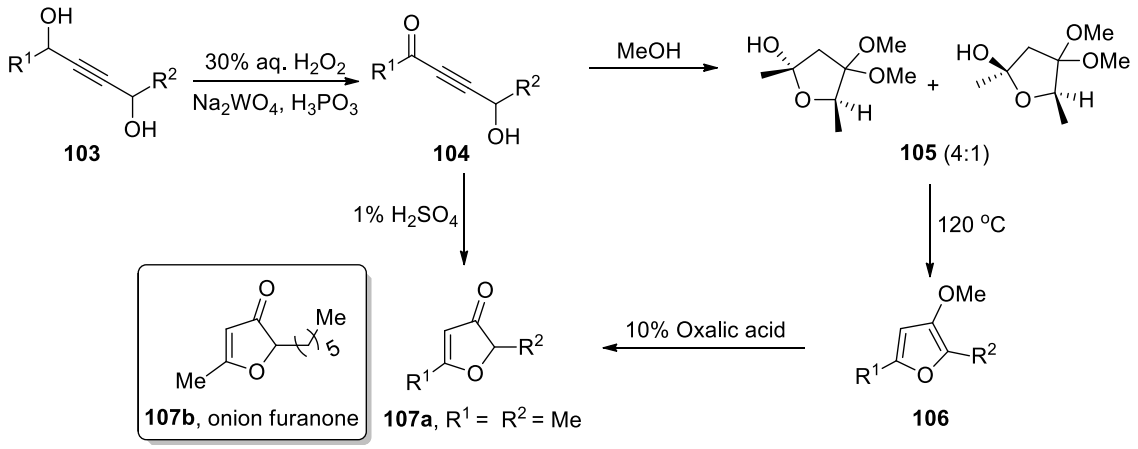
1.4.6 Synthesis of 2,5-disubstituted-3(2*H*)-furanones

Curran and Singleton reported a synthetic strategy for the synthesis of 2,5-disubstituted-3(2*H*)-furanones which involved a dipolar cycloaddition. It started with the cycloaddition of nitrile oxides to enol ethers **99** to synthesize substituted isoxazolines **100** which upon Raney-Ni mediated reduction followed by acid catalysed cyclisation afforded the corresponding 2,5-disubstituted-3(2*H*)-furanones **102**. (Scheme 1.17).[37]



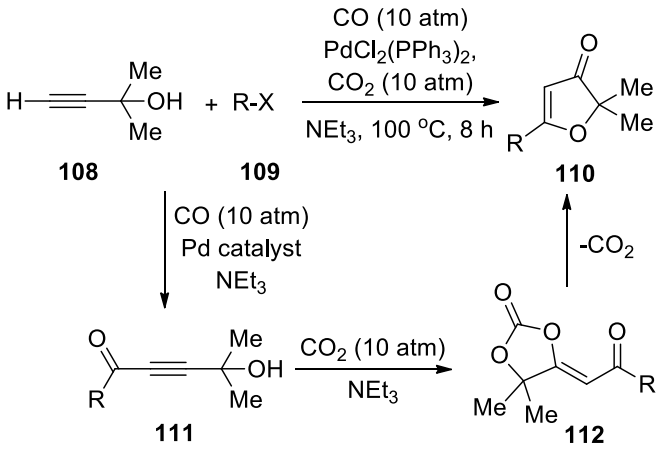
Scheme 1.17

In 1986, Thomas et al. reported the synthesis of 2-hexyl-5-methyl-3(2*H*)-furanone **107b** otherwise known as 'onion furanone' (Scheme 1.18).[38] The synthesis commenced with the tungstate ion catalyzed oxidation of the acetylenic diol **103** with hydrogen peroxide followed by an acid catalyzed cyclisation.



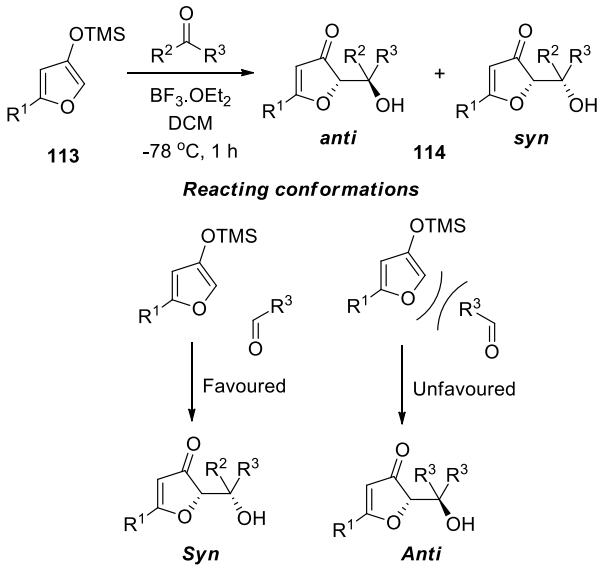
Scheme 1.18

In 1989 Inoue and co-workers reported a facile method for the synthesis of 2,5-disubstituted 3(*2H*)-furanones from propargylic alcohols **108**, CO and organic halides **109** using transition metal catalysis under an atmosphere of CO_2 (Scheme 1.19).[39] The methodology was utilized for the synthesis of disubstituted 3(*2H*)-furanones **110** in moderate yields by changing the substituent at the 5th position.



Scheme 1.19

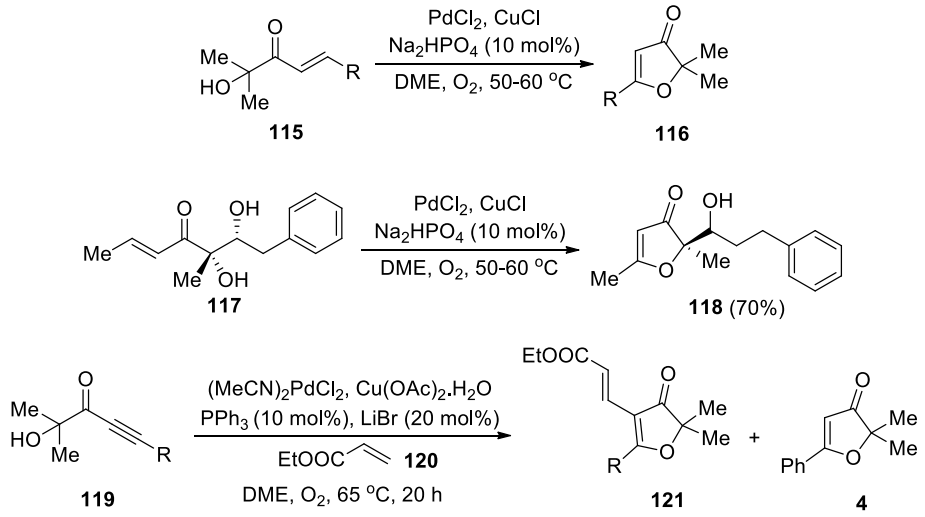
An interesting Lewis acid catalyzed stereoselective aldol reaction of 3-silyloxyfurans **113** with aldehydes for the synthesis of 2,5-disubstituted-3(2*H*)-furanones has been reported by Winkler and co-workers (Scheme 1.20).[40] An increase in the diastereoselectivity of the aldol reaction was noted with increasing steric hindrance of the aldehyde. In this line, it was found that the reactions with isobutyraldehyde and pivaldehyde showed a higher diastereoselectivity, whereas with sterically unhindered aldehydes such as *n*-hexanal only modest diastereoselectivity was detected. The observed diastereoselectivity is due to the aldol reaction that proceeds *via* the conformer which is sterically unhindered.



Scheme 1.20

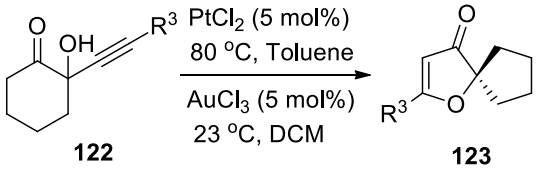
A synthetic route leading to spirocyclic 3(2*H*)-furanones was introduced by Kirsch and co-workers in 2006.[41] The methodology involved either a Au(III) or a Pt(II) catalyzed domino reaction for the synthesis of the 2,5-disubstituted-3(*2H*)-furanone. The reaction proceeded *via*

transition metal catalyzed activation of the alkyne functionality in the starting 2-hydroxy-2-alkynyl carbonyl compounds **115** followed by a heterocyclization and 1,2-migration. It was found that the reactions catalyzed by Au(III) salts provided higher yields but were restricted to aryl substituents. In contrast, Pt(II) salts catalyzed the domino reactions with substrates bearing both alkyl and aryl substituents. This approach to spirocyclic compounds is not only limited for accessing five-membered spirocyclic ring systems but also applicable to cycloheptanone and cyclooctanone, which undergo ring contraction to give the corresponding (cyclohexyl and cycloheptyl) spirocycles. Furthermore, acyclic systems also reacted by migration of alkyl and aryl groups (Scheme 1.21).



Scheme 1.21

Another Pt-catalyzed cyclization strategy for the synthesis of 2,5-disubstituted-3(*2H*)-furanones from propargyl alcohols was reported by in 2008.[42] The reaction was well tolerated by different substituted propargyl alcohols **122** from which the corresponding furanones were obtained in moderate to good yields. (Scheme 1.22).

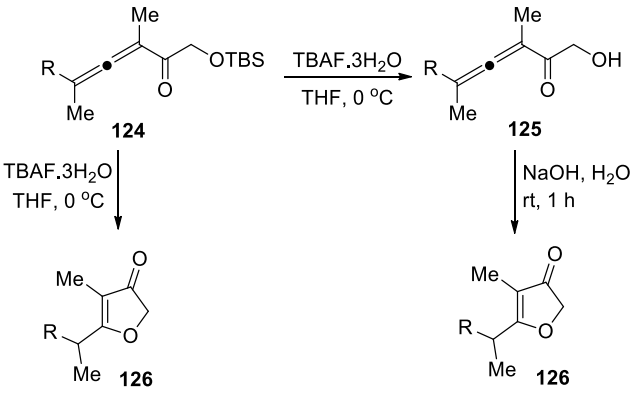


Scheme 1.22

1.4.7 Synthesis of 4,5-disubstituted-3(2*H*)-furanones

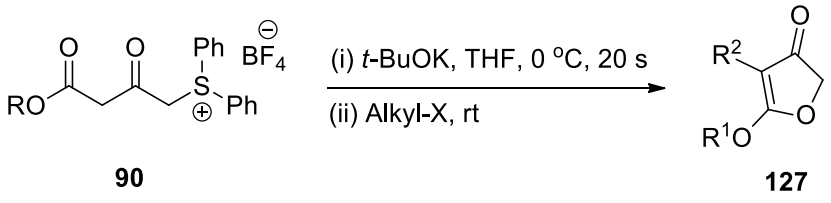
In 2011, Ponooth et al. revealed a strategy for accessing 4,5-disubstituted-3(2*H*)-furanones by the cycloisomerization of bifunctionalized allenes (Scheme 1.23).[43] The allene scaffold was

cleverly designed by placing the keto and hydroxyl groups in such positions that a base induced cyclisation would result in a substituted 3(2*H*)-furanone moiety. The phenyl (or benzyl)-substituted allenone (TBS protected) **124** was then treated with TBAF at 0°C initiating a deprotection-cyclisation cascade affording the 4,5-disubstituted-3(2*H*)-furanone **126** in good yield. Interestingly, the TBS-deprotection of alkyl-substituted allenones afforded hydroxy allenones **125** as the sole products. These alkylated hydroxyl allenones furnished substituted 3(2*H*)-furanones on treatment with aqueous NaOH. The proposed mechanism proceeds by an intramolecular oxa-Michael addition (*5-endo-dig*) and subsequent base-catalyzed isomerization of the exocyclic double bond.



Scheme 1.23

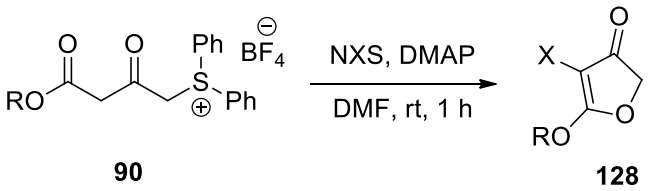
Kawano and co-workers reported an interesting method for the synthesis of 4-alkyl-5-alkoxy-3(2*H*)-furanones by an alkylative intramolecular cyclization protocol (Scheme 1.24). In this approach, the authors utilized diphenylsulfonium tetrafluoroborate as the leaving group on the acetoacetate moiety. When 4-diphenylsulfonium acetoacetate **90** was treated with benzylbromide and a base in THF, the corresponding 4-benzyl-substituted 3(2*H*)-furanone **127** was formed.[44]



Scheme 1.24

Soon after, the same authors reported a similar approach towards 4-halo-5-alkoxy-3(2*H*)-furanones (Scheme 1.25). This halogenative intramolecular cyclization strategy was also effected by using diphenylsulfonium tetrafluoroborate as the leaving group. In this case, 4-

diphenylsulfonium acetoacetate **90** was treated with *N*-halosuccinimde and DMAP in DMF at rt and the corresponding 4-halo-substituted 3(2*H*)-furanone **128** was formed. Irrespective of the alkyl or aryl substituent on the ester group of the acetoacetate, the reaction worked well with NIS and NBS affording the respective products in good yields.[45]

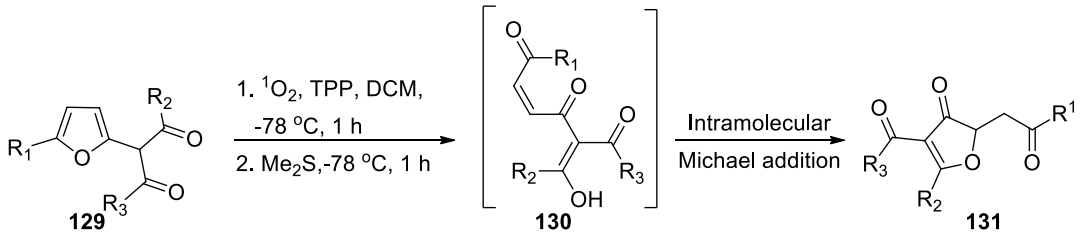


90 **128**

Scheme 1.25

1.4.7 Synthesis of 2,4,5-trisubstituted-3(2*H*)-furanones

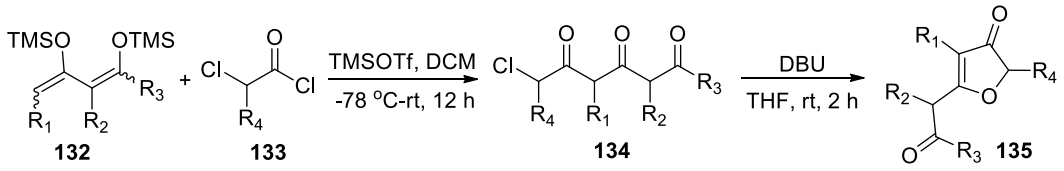
In 1988, a singlet oxygen mediated synthesis of functionalized 3(2*H*)-furanones **131** was reported by Scettri and co-workers from 2-(2-furyl)-1,3-dicarbonyl compounds (Scheme 1.26).[75] The sequence was effected by photoirradiation (with a 300 W lamp) of 2-(2-furyl)-1,3-dicarbonyl compounds **129** in the presence of tetraphenylporphyrin at -78°C for 1 h. These authors effectively utilized the developed methodology for the synthesis of a naturally occurring metabolite of *Penicilliumviridicaticum*, (±)-viridicatic acid.[46]



129 **130** **131**

Scheme 1.26

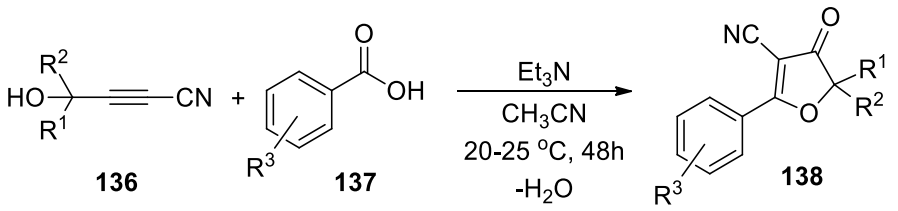
A chemo- and regioselective pathway for the synthesis of 2,4,5-trisubstituted-3(2*H*)-furanone was reported in 2000 by Langer and Krummel (Scheme 1.27). These authors found that when synthons of 1,3-dicarbonyl compounds were treated with chloroacetyl chloride under Lewis acid catalysis conditions, 6-chloro-3, 5-dioxoesters were formed which could be easily converted to trisubstituted-3(2*H*)-furanones by treatment with a base.[47]



132 **133** **134** **135**

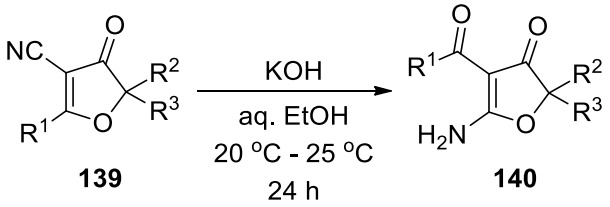
Scheme 1.27

In 2010, Trofimov and co-workers described the synthesis of 4-cyano-3(2*H*)-furanones **138** from *α, β*-acetylenic-*γ*-hydroxy nitriles **136** and arene carboxylic acids **137** under metal free conditions (Scheme 1.28). The reaction was found to be general with a range of substituted acetylenes and arene carboxylic acids.[48]



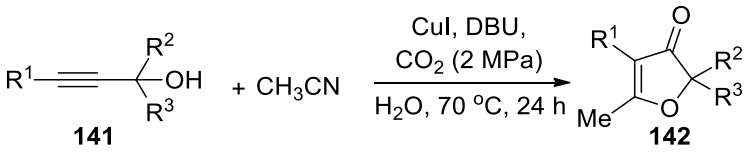
Scheme 1.28

Shemyakina and co-workers effectively utilized the previously reported 4-cyano-3(2*H*)-furanones for the synthesis of 5-amino-3(2*H*)-furanones by a base catalyzed ring-cleavage and recyclization pathway (Scheme 1.29). The reaction was monitored by IR spectroscopy specifically by following the disappearance of the C=C–C≡N bands at 2230–2211cm^{-1}.[49]



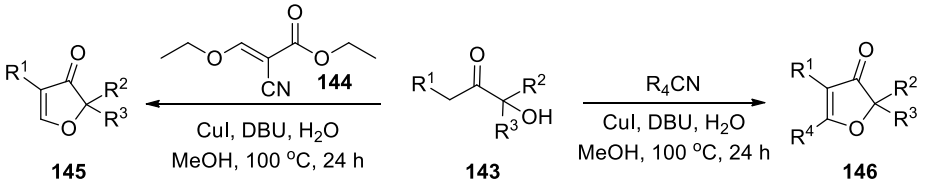
Scheme 1.29

Another CO_2 mediated and Cu-catalyzed one-pot reaction for the synthesis of highly substituted 3(*2H*)-furanones from nitriles and propargylic alcohols was reported in 2011 (Scheme 1.30). In this transformation, one of the two oxygen atoms of carbon dioxide is incorporated into the 3(2*H*)-furanone moiety. The nitrile acts as both the reactant and solvent. Moreover, copper salts also have dual roles in activating both the propargylic alcohol and the nitrile. The reaction was found to be general for a range of substituted propargylic alcohols with aryl and heteroaryl substiutents.[50]



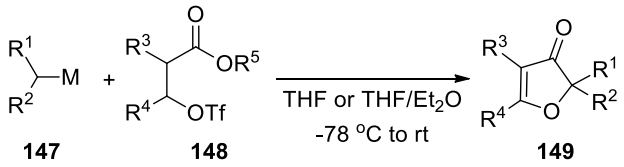
Scheme 1.30

Later, the same group reported a CuI/DBU mediated synthesis of a wide range of highly substituted 3(2*H*)-furanones by catalytic [4+1] annulation of *α*-hydroxy ketones and nitriles (Scheme 1.31). (Ethoxymethylene)cyanoacetate **144** was used as an HCN equivalent for the synthesis of 2,4-disubstituted-3(2*H*)-furanone **145** as well. The catalytic annulation was found to be general with different substituted arylnitriles and *α*-hydroxy ketones.[51]



Scheme 1.31

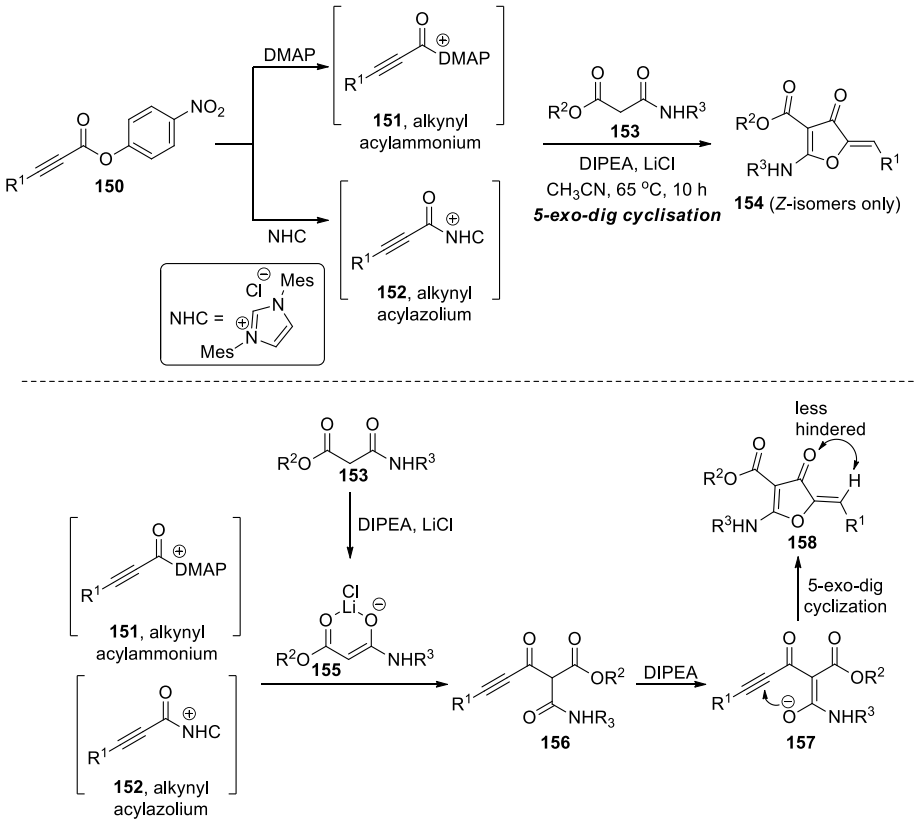
In 2016, Dieter and co-workers published the synthesis of bis-heterocyclic spiro 3(2*H*)-furanones **149** from *β*-keto esters or 2-carboalkoxy phenols and *α*-heteroatom-stabilized carbanions (Scheme 1.32). The reaction was carried out by treating an organometallic reagent (2.0 equiv. of RMgX or RLi) and an enol or phenol triflate (2.0 equiv.) in THF (or THF/Et_2O mixture) at -78 °C to rt. By utilizing the developed methodology, the authors could synthesize both 2,4,5-trisubstituted and 2,5-disubstitued-3(2*H*)-furanones in moderate to good yields.[52]



Scheme 1.32

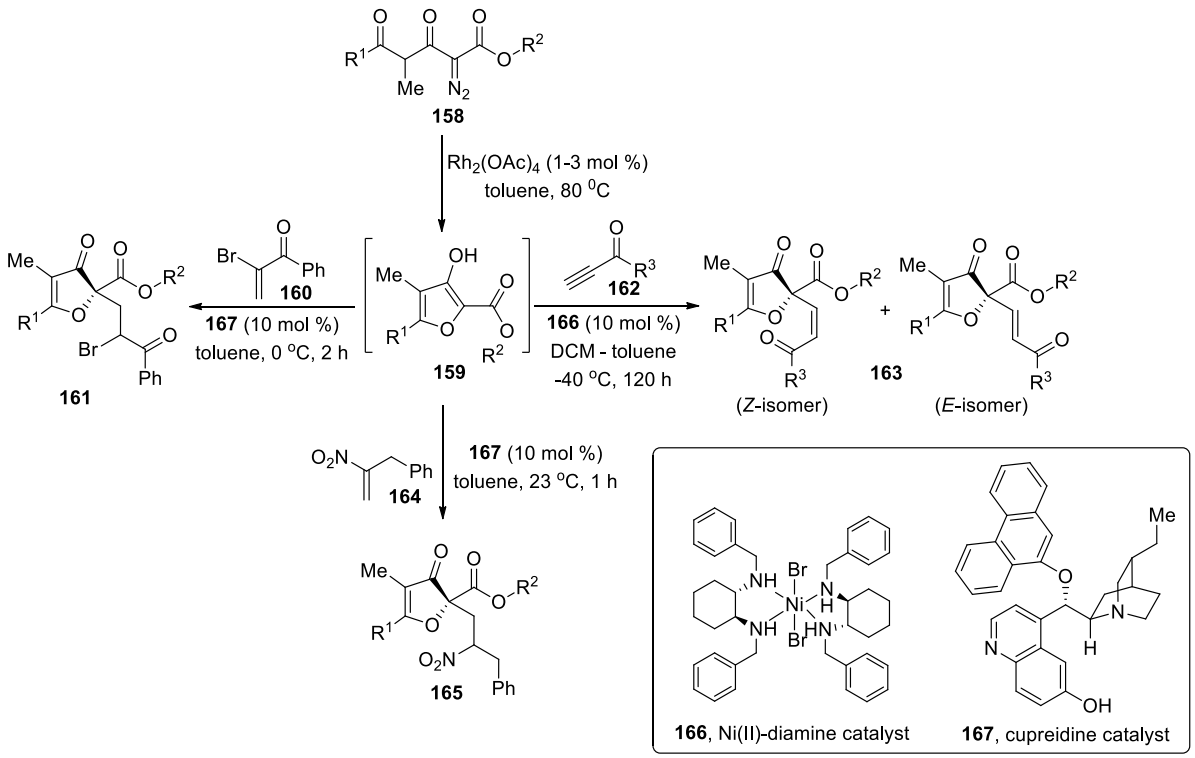
A highly regio-and stereoselective synthesis for (*Z*)-5-amino-3(2*H*)-furanone by a Lewis base/Lewis acid cooperative catalysis was developed in 2017 (Scheme 1.33).[53] In this report, alkynyl esters **150** were employed as precursors of *α, β*-unsaturated alkynyl acyl ammonium **151** and azolium precursors **152** which under cooperative catalysis conditions undergo a [2+3] annulation with amidomalonates **153** furnishing 2,4,5-trisubstituted-3(2*H*)-furanones **154**. The reaction proceeds *via* the initial formation of the acyl ammonium intermediate **151** or acyl azolium intermediate **152** by a nucleophilic attack of the ester with DMAP or NHC.[87] The activated amidomalonate **155** generated from **154** with DIPEA/LiCl then adds to intermediates in a 1,2-fashion generating **156**. The enolate anion produced from **156** by base treatment subsequently undergoes a 5-*exo-dig* cyclization to furnish the final product. The regioselectivity of the reaction was attributed to the charge distribution in the intermediates and

the high stereoselectivity leading to the exclusive formation of *Z*-isomers was rationalized in terms of less steric interaction between the alkenyl hydrogen atom and the carbonyl group (Scheme 1.33).



Scheme 1.33

A Ni(II)−diamine complex or cupreidine catalysed enantioselective conjugate addition of *in situ* generated 2-alkoxycarbonyl-3(2*H*)-furanones to electrophiles such as terminal alkynones, *α*-bromo enones, and *α*-benzyl nitroalkenes was reported in 2018 (Scheme 1.34).[54] A Rh(II)-catalyzed cyclization of the *α*-diazo carbonyl precursor **158** was suggested for the generation of furanone intermediate **159.** The Ni(II)−diamine complex **166** catalyzed conjugate addition of 2-alkoxycarbonyl-3(2*H*)-furanone to the terminal alkynone **162** preferentially gave the *Z*-isomer of 2,4,5-trisubstituted-3(2*H*)-furanone in up to 79 % in yield and enantiomeric ratio (e.r.) of 98:2.



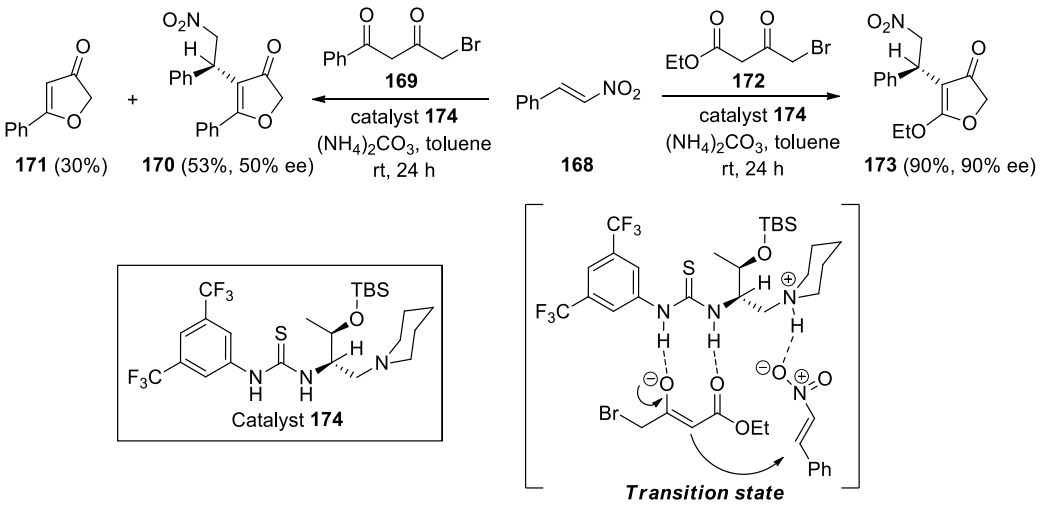
Scheme 1.34

The enantioselectivity of the reaction depends inversely on the temperature (e.r. = 88:12 at 23°C, e.r. = 94:6, at −20 °C, e.r. = 98:2 at −40 °C). The enantioselective 1,4-addition of 2-alkoxycarbonyl-3(2*H*)-furanones with other π-electrophiles such as *α*-bromoenone **160** and *α*-benzyl nitroalkene **164** was catalyzed by a cupreidine derivative **167**.

1.5 Synthesis of 3(2*H*)-furanones from 4-Halo-1, 3-dicarbonylcompounds

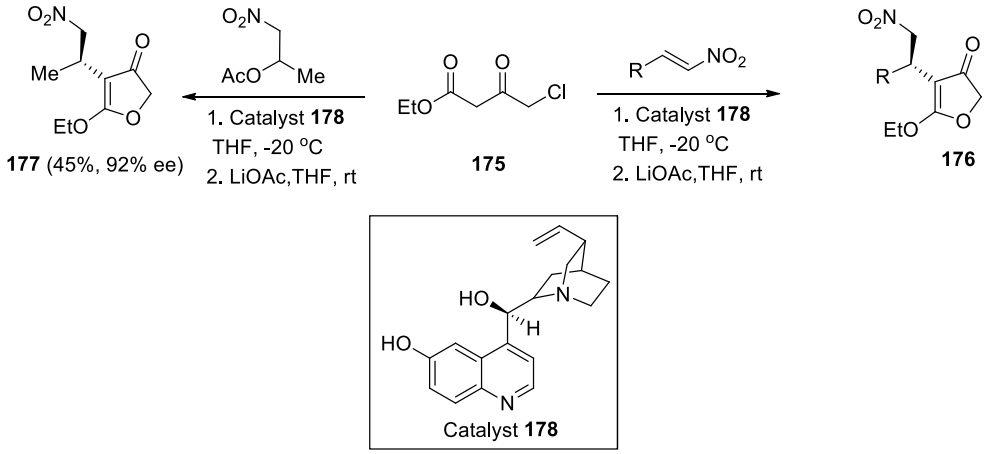
The first report on the utilization of 4-halo-1,3-dicarbonylcompounds as precursor for 3(2*H*)-furanones synthesis was reported by Lu and co-workers in 2012. They designed a modified Feist–Bénary reaction for the asymmetric synthesis of 4,5-disubstituted-3(2*H*)-furanones. The reaction was performed with ethyl 4-bromoacetoacetate **172** and nitroolefin **168** in the presence of L-threonine-derived tertiary amine/thioureaas chiral catalyst and $(NH_4)_2CO_3$ as the base. The reaction was also tried with 4-bromo-1-phenylbutane-1,3-dione **169** and nitrostyrene **168** under the conditions mentioned above. This reaction resulted in furnishing the expected product in moderate yields and an *ee* of 50% along with a self-cyclization product **171** of 4-bromo-1-diketone. The authors proposed a plausible transition state model which demonstrates the deprotonation of the *β*-ketoester to the enolate by the tertiary amine group of the catalyst. This moiety engages in hydrogen-bonding interactions with the thiourea moiety of the catalyst. In addition, the authors claim that the substrate binding was effected by the

ionic interaction between the positively charged ammonium with the nitroolefin (scheme 1.35).[55]



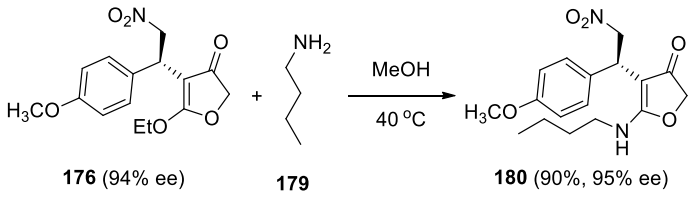
Scheme 1.35

Soon after, Yan *et al*. reported another organocatalytic asymmetric approach towards 4,5-disubstituted-3(2*H*)-furanones. In this report, they used 6'-demethyl quinine as the chiral catalyst for effecting the asymmetric Michael addition of 4-haloacetoacetate to the nitroolefin. An additional base, LiOAc was used for inducing the intramolecular cyclisation in the Michael adduct towards the substituted 3(2*H*)-furanone. The authors also tried the reaction of 2-acetyloxy-1-nitro-propane with ethyl 4-chloro-acetoacetate. The reaction was explained to proceed *via* the *in-situ* formation of (*E*)-1-nitroprop-1-ene (from 2-acetyloxy-1-nitro-propane) onto which 4-chloro-acetoacetate underwent the tandem Michael addition-intramolecular cyclization affording tetronicacid derivative in lower yield, but in good enantioselectivity (Scheme 1.36).[56]



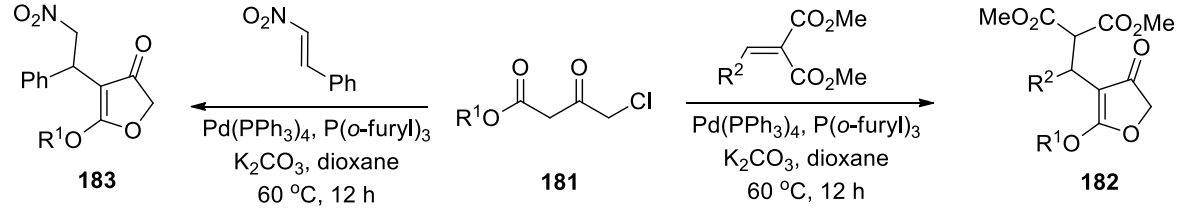
Scheme 1.36

The authors have synthesized aza-prostaglandin analogue **180** by treating 3(2*H*)-furanone **176** with butylamine **179** in MeOH at 40 °C (Scheme 1.37).



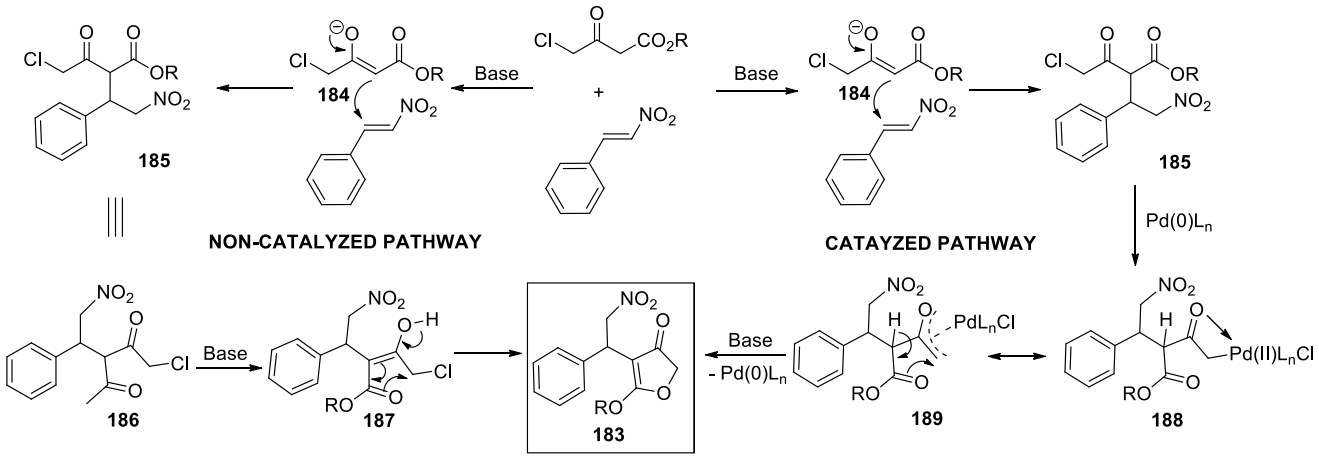
Scheme 1.37

In 2013, we came across a serendipitous observation of 3(2*H*)-furanone formation instead of an expected cyclopentenone moiety (scheme 1.38). From the Pd-catalyzed reaction of activated styrene and 4-haloacetoacetate in the presence of a base, we isolated 4,5-disubstituted-3(2*H*)-furanone. Under the optimized condition which consisted of $Pd(PPh_3)_4$ as catalyst, P(*o*-furyl)$_3$ as ligand, K_2CO_3 as base and dioxane as solvent, the reaction was found to be general for a range of aromatic and aliphatic activated alkenes. The reaction was also found to proceed in the absence of any Pd-catalyst, but with lower yields.[57]



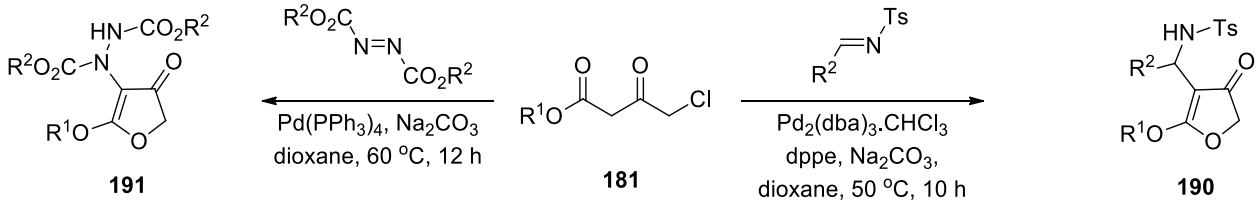
Scheme 1.38

The mechanisms of both catalyzed and uncatalyzed reactions involve two stages (Scheme 1.39). The first one being the Michael addition of acetoacetate to the activated styrene. The second stage of the catalyzed process starts with the oxidative addition of Pd(0) to the C-Cl bond resulting in the oxy-π-allyl Pd-intermediate **189.** This is followed by the abstraction of the acidic proton by base and the ester enolate attacks the carbon end of the oxy-π-allyl Pd-intermediate resulting in the formation of 3(2*H*)-furanone ring. In the uncatalyzed pathway, the ester enolate in the Michael adduct **186** displaces the chlorine forming the furanone moiety.



Scheme 1.39

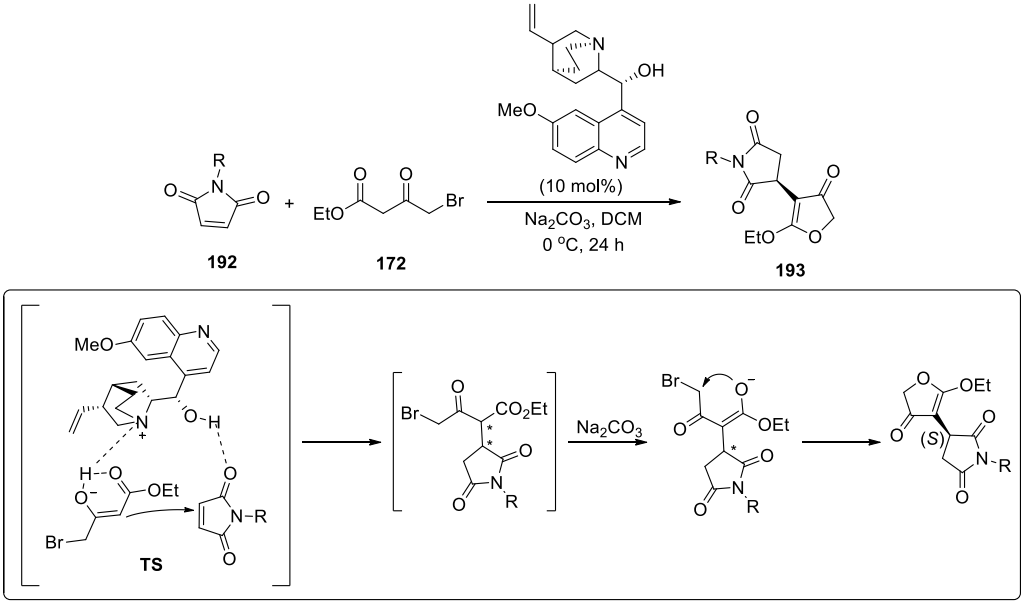
In 2014, we extended the methodology for introducing different substituents to the 4th position of the 3(2*H*)-furanone ring. This was effected by making use of electrophiles such as activated imines and dialkylazodicarboxylates (Scheme 1.40). The tandem process was found to be general with a variety of tosylimines furnishing the corresponding 4-substituted furanones in good to excellent yields in the presence of a combination of $Pd_2(dba)_3.CHCl_3$ as catalyst, dppe as ligand and Na_2CO_3 as base. 4-Hydrazino-3(2*H*)-furanones were obtained in excellent yields by the reaction of 4-haloacetoacetate and dialkylazodicarboxylates in the presence of $Pd(PPh_3)_4$ as catalyst and K_2CO_3 as base.[58]



Scheme 1.40

Another report on the utilization of 4-haloacetoactate for the asymmetric synthesis 4,5-disubstituted-3(2*H*)-furanones came from the group of Yu. In the presence of commercially available quinine catalyst and Na_2CO_3 as base, ethyl 4-bromo-acetoacetate was treated with *N*-substituted maleimide in DCM at 0 ^oC to afford succinimide substituted 3(2*H*)-furanone (Scheme 1.41). The reaction proceeds *via* the TS where the hydroxyl group of the catalyst activates maleimide through hydrogen bonding with the tertiary amine of quinine which activates the enol form of acetoacetate. This is followed by the Michael addition of the enolate to the maleimide from Re-face. The Michael adduct then undergoes a base induced

intramolecular *O*-alkylation to generate the disubstituted-3(2*H*)-furanone in (*S*)-configuration.[59]



Scheme 1.41

1.6 Conclusion and present work

Developing new and efficient synthetic methodologies for the synthesis of new heterocyclic compounds with biological significance is always considered as a challenge to organic chemists. The first report on the synthesis of 3(2*H*)-furanone derivatives appeared in 1958; after which several research groups worked and published methods for accessing this heterocycle. Initially, all efforts were centered on the total synthesis of 3(2*H*)-furanone containing natural products. The interesting biological properties exhibited by these motifs fueled research on developing methods for the preparation of appropriately functionalized 3(2*H*)-furanones. In the past five decades, several new synthetic routes were reported for installing substituents at predetermined positions by starting from cleverly designed substrates. These methods involved the use of acids or bases as catalysts or in stoichiometric amounts, several organocatalysts, metal catalysts etc. Many tandem processes were also introduced for making 3(2*H*)-furanone derivatives available. Several synthetic chemists were also successful in the enantioselective synthesis of complex natural products and other substituted 3(2*H*)-furanones. The mechanistic rationalizations of the reactions mentioned above, leave something to be desired, both from the theoretical and the experimental point of view. We believe that there is still large scope for developing new methods towards functionalized 3(2*H*)-furanones. Sustainable chemistry aspects are lacking in most of the reported preparative methods and

validation of the reactions on a bulk scale is also missing. There are many 3(2*H*)-furanone containing natural products which have not been accessed by total synthesis. By using modern computational techniques new 3(2*H*)-furanone derivatives with specific biological properties could be designed and eventually be synthesized.4-halo-1,3-dicarbonyl compounds are interesting synthons for the synthesis of 3(2*H*)-furanones. The active methylene nucleophile generated from 4-halo-1,3-dicarbonyl compounds which can be trapped by a electrophile and subsequent intramolecular cyclisation is a promising method for the synthesis of the 4-substituted 3(2*H*)-furanones. Futher derivitastion is also possible by starting with appropriately functionalized 4-halo-1,3-dicarbonyl compounds or electrophile. As part of the doctaral study, we tried to explore the design and synthesis of different substituted 3(2*H*)-furanones from 4-halo-1,3-dicarbonyl compounds, wherein we mainly foccused on developing protocols for trapping the carbanion generated from 4-halo-1,3-dicarbonyl compounds with various electrophiles such as alkynes, benzynes and diazabicyclic olefins.

Chaper 2 disusses about the reaction of 4-halo-1,3-dicarbonyl compounds with alkynes, where we have observed the formation of 4-vinyl-3(2*H*)-furanone formation along with its regioisomer, irrespective of our expection of E/Z stereoisomers. The reaction proceeds *via* a tandem Michael addition and an intramolecular cyclization pathay. The formation of its regioisomer takes place *via* a stepwise [2+2] cycloaddition between enolate (of the 4-halo-1,3-dicarbonyl compound) and activated alkyne followed by a sequential 4π-ring opening and an intramolecular cyclization. Another interesting observation was the formation of 3(2*H*)-furanone fused 2-pyridone from the reaction of 4-bromo-3-oxo-*N*-alkyl (aryl)butanamide with activated alkynes.

Chapter 3 outlines the development of a mild and metal free approcach towards the synthesis of 4-aryl-3(2*H*)-furanones from our synthon 4-halo-1,3-dicarbonyl compound and benzyne precursor. The reaction proceeds *via* the nucleophilic addition of an active methylene compound to the aryne followed by ring closing of the adduct. Further derivatisation was done by synthesizing different heterocyclic analogues of aza-prostaglandins from 4-phenyl-3(2*H*)-furanones. The reaction pathway was further confirmed with a DFT calculation using M06L/SMD/6-311G(d,p) level density functional theory.

Transition metal catalyzed desymmetrization of diazabicyclic olefins *via* ring opening with active methylene nucleophiles generated from 4-halo-1,3-dicarbonyl compound was investigated in **Chapter 4.** Palladium catalyzed desymmetrization of diazabicyclic olefins *via* ring opening with active methylene nucleophile generated from 4-halo-1,3-dicarbonyl

compound was also investigated. Desymmetrization of diazabicyclic olefins is an interesting and well explored area, while the reactivity of soft nucleophiles with the same is the least studied one. We have observed an interesting stereoselective synthesis of 3(2*H*)-furanones appended-1,3-*cis*-disubstituted cyclopentene from diazabicyclic olefin and 4-halo-1,3-dicarbonyls. The reaction proceeds *via* the formation of a π-allylpalladium intermediate which is attacked by the active methylene species and an intramolecular nucleophilic substitution in the 4-halo-1,3-dicarbonyl moiety. We could extend this methodology to cyclopropane-appended spirotricyclic olefin for synthesizing 3(2*H*)-furanone substituted spiro[2.4]hept-5-ene. We have also designed and tried an intramolecular Heck reaction for accessing a new class of 3(2*H*)-furanone fused tetrahydroazocine derivatives from an appropriately functionalized azaprostaglandin analogue.

1.7 References

1. a) D. W. Henry, R. M. Silverstein, *J. Org. Chem*. **1966**, *31*, 2391.
   b) Y. Li, K. J. Hale, *Org. Lett*. **2007**, *9*, 1267.
   c) D. C. Sass, V. C. G. Heleno, J. L. C. Lopes, M. G. Constantino, *Tetrahedron Lett.* **2008**, *49*, 3877.
2. A. Husain, S. A. Khan, F. Iram, Md. A. Iqbal, M. Asif, *Eur. J. Med. Chem.* **2019**, *171*, 66.
3. C. W. Brandt, W. I. Taylor, B. R. Thomas, *J. Chem. Soc.* **1954**, 3245.
4. W. Parker, R. A. Raphael, D. I. Wilkinson, *J. Chem. Soc.* **1958**, 3871.
5. S. M. Kupchan, C. W. Sigel, M. J. Matz, J. A. S. Renauld, R. C. Haltiwanger, R. F. Bryan, *J. Am. Chem. Soc.* **1970**, *92*, 4476.
6. F. N. Lahey, J. K. Macleod, *Aust. J. Chem.* **1967,** *20*, 1943.
7. D. L. Dreyer, A. Lee, *Phytochemistry* **1972**, *11*, 763.
8. C. Qi, L. Huang, G. Yuan, Y. Ren, H. Jiang, *Org. Lett.* **2011**, *13*, 5520.
9. H. He, C. Qi, X. Hu, L. Ouyang, W. Xiong, H. Jiang, *J. Org. Chem.* **2015**, *80*, 4957.
10. J. Cao, K. Sun, S. Dong, T. Lu, Y. Dong, D. Du, *Org. Lett.* **2017**, *19*, 6724.
11. P. Vojackova, D. Chalupa, J. Prieboj, M. Necas, J. Svenda, *Org. Lett.* **2018**, *20*, 7085.
12. S. Manfredini, D. Simoni, R. Ferroni, R. Bazzanini, S. Vertuani, S. Hatse, J. Balzarini, E.D. Clercq, *J. Med. Chem.* **1997**, *40*, 3851.
13. S. Chimichi, M. Boccalini, B. Cosimelli, F.D. Acqua, G. Viola, *Tetrahedron,***2003**, *59*, 5215.
14. K. Mal, A. Sharma, P.R. Maulik, I. Das, *Chem. Eur J.* **2014**, *20*, 662.

15. T. Irie, T. Asami, A. Sawa, Y. Uno, M. Hanada, C. Taniyama, Y. Funakoshi, H. Masai, M. Sawa, *Eur. J. Med. Chem.* **2017**, *130*, 406.
16. T. Raab, J. A. Lo′pez-Ráez, D. Klein, J. L. Caballero, E. Moyano, W. Schwab, J. Muñoz-Blancob, *Planta Cell* **2006**, *18*.
17. N. Nunomuraa, M. Sasakia, Y. Asaoa, T. Yokotsukaa, *Agric. Biol. Chem.* **1976**, *40*, 491.
18. L. Re, B. Maurer, G. Ohlofl′, *Helv. Chim. Acta.* **1973**, *56*, 1882.
19. M. Sasaki, N. Nunomura, T. Matsudo, *J. Agric. Food Chem.* **1991**, *39*, 934.
20. J. C. Slaughter, *Biol. Rev.* **1999**, *74*, 259.
21. I. Blank, L. B. Fay, *J. Agric. Food Chem.* **1996**, *44*, 53.
22. T. Hauck, F. Bruhlmann, W. Schwab, *Appl. Environ. Microbiol.* **2003**, *69*, 3911.
23. T. Haucka, Y. Hubnera, F. Bruhlmannb, W. Schwab, *Biochim. Biophys. Acta Gen. Subj.* **2003**, *1623*, 109.
24. M. Ohata, K. Kohama, Y. Morimitsu, K. Kubota, E. Sugawara, *Biosci. Biotechnol. Biochem.* **2007**, *71*, 407.
25. T. Brandt, W. I. Taylor, *J. Chem. Soc.* **1954**, 3425.
26. A. B. Smith III, P. A. Levenberg, P. J. Jerris, R. M. Scarborough Jr., P. M. Wovkulich, *J. Am. Chem. Soc.* **1981**, *103*, 1501.
27. Ch. Meister, H. D. Scharf, *Synthesis* **1981**, 737.
28. L. Camici, A. Ricci, M. Taddei, *Tetrahedron Lett.* **1986**, *27*, 5155.
29. F. Sher, J. L. Isidor, H. R. Taneja, R. M. Carlson, *Tetrahedron Lett.* **1973**, *14*,577.
30. H. Saimoto, M. Shinoda, S. Matsubara, K. Oshima, T. Hiyama, H. Noazki, *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3088.
31. J. Chen, R. Properzi, D. P. Uccello, J. A. Young, R. G. Dushin, J. T. Starr, *Org. Lett.* **2014**, *16*, 4146.
32. P. X. Iten, A. A. Hofmann, C. H. Eugster, *Helv. Chim. Acta* **1978**, *61*, 430.
33. P. G. Baraldi, A. Barco, S. Benetti, S. Manfredini, G. P. Pollini, D. Simoni, *Tetrahedron* **1987**, *43*, 235.
34. B. Varghese, S. N. Al-Busafi, F. E. O. Suliman, S. M. Z. Al-Kindy, *New J. Chem.* **2015**, *39*, 6667.
35. S. Inagaki, M. Ukaku, A. Chiba, F. Takahashi, Y. Yoshimi, T. Morita, T. Kawano, *J. Org. Chem.* **2016**, *81*, 8363.
36. S. Inagaki, K. Saito, S. Suto, H. Aihara, A. Sugawara, S. Tamura, T. Kawano, *J. Org. Chem.* **2018**, *83*, 13834.

37. D. P. Curran, D. H. Singleton, *Tetrahedron Lett.* **1983**, *24*, 2079.
38. A. F. Thomas, H. Damm, *Tetrahedron Lett.* **1986**, *27*, 505.
39. Y. Inoue, K. Ohuchi, I-Fang Yen, S. Imaizumi, *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3518.
40. J. D. Winkler, K. Oh, S. M. Asselin, *Org. Lett.* **2005**, *7*, 387.
41. St. F. Kirsch, J. T. Binder, C. Liébert, H. Menz, *Angew. Chem. Int. Ed*. **2006**, *45*, 5878.
42. E. M. Bunnelle, C. R. Smith, S. K. Lee, S. W. Singaram, A. J. Rhodes, R. Sarpong, *Tetrahedron*. **2008**, *64*, 7008.
43. M. Poonoth, N. Krause, *J. Org. Chem.* **2011**, *76*, 1934.
44. S. Inagaki, K. Saito, S. Suto, H. Aihara, A. Sugawara, S. Tamura, T. Kawano, *J. Org. Chem.* **2018**, *83*, 13834.
45. S. Inagaki, M. Nakazato, N. Fukuda, S. Tamura, T. Kawano, *J. Org. Chem.* **2017**, *82*, 5583.
46. R. Antonioletti, F. Bonadies, T. Prencipe, A. Scettri, *J. Chem. Soc. Chem.Commun.* **1988**, 850.
47. a) Th. Krummel, P. Langer, *Chem. Commun*. **2000,** 967, b) Th. Krummel, P. Langer, *Chem. Eur. J.* **2001**, *7*, 1720.
48. B. A. Trofimov, O. A. Shemyakina, A. G. Mal'kina, I. A. Ushakov, O. N. Kazheva, G. G. Alexandrov, O. A. Dyachenko, *Org. Lett.* **2010**, *12*, 3200.
49. O. G. Volostnykh, O. A. Shemyakina, A. V. Stepanov, I. A. Ushakov, T. N. Borodina, *Synthesis*. **2018**, *50*, 4905.
50. C. Qi, L. Huang, G. Yuan, Y. Ren, H. Jiang, *Org. Lett*. **2011**, *13*, 5520.
51. H. He, C. Qi, X. Hu, L. Ouyang, W. Xiong, H. Jiang, *J. Org. Chem.* **2015**, *80*, 4957.
52. A. Picado, S. J. Li, R. K. Dieter, *J. Org. Chem*. **2016**, *81*, 1391.
53. J. Cao, K. Sun, S. Dong, T. Lu, Y. Dong, D. Du. *Org. Lett.* **2017**, *19*, 6724.
54. P. Vojackova, D. Chalupa, J. Prieboj, M. Necas, J. Svenda, *Org. Lett.* **2018**, *20*, 7085.
55. X. Dou, X. Han, Y. Lu, *Chem. Eur. J.* **2012**, *18*, 85.
56. Y. Yan, R. Lu, J. Wang, Y. Xuan, M. Yan, *Tetrahedron.* **2010**, *68*, 6123.
57. J. John, H. Hopf, Eur. *J. Org. Chem.* **2013**, 841.
58. J. John, E. Târcoveanu, P. G. Jones, H. Hopf, *Beilstein J. Org. Chem*. **2014**,*10*, 1462.
59. J. Zhou, L. Bai, G. Liang, Y. Chen, Z. Gan, W. Wang, H. Zhou, Y Yu, *RSC Adv.* **2017**, *7*, 39885.

Chapter 2

Tandem Reaction of 4-Halo-1,3-dicarbonyl Compounds with Alkynes towards 4-Vinyl-3(2*H*)-Furanones and Furanone fused 2-Pyridones

2.1 Introduction

Alkynes with an electron withdrawing group at terminal position (i.e., activated alkynes) are useful synthetic precursors due to the combination of good bench stability and high reactivity (Fig 2.1). These moieties are widely accepted as dienophiles in cycloaddition reactions and as nucleophiles in conjugate addition reactions. Alkynes in conjugation with carbonyl moieties such as ketones (ynones), esters (propiolates), or amides (propiolamides) undergo nucleophilic attack easily to furnish either a 1,2-addition product (at the carbonyl carbon) or a 1,4-addition product (at the acetylenic moiety) (scheme 2.1). The former reaction is usually induced by hard or strong nucleophiles, including organometallic reagents such as organolithium or Grignard reagents, while the latter is achieved with soft nucleophiles. The 1,4-conjugate addition reaction, otherwise called as the "Michael addition" or "Michael reaction", remains as a useful synthetic pathway in organic synthesis for heterocyclic, combinatorial and multicomponent chemistry.[1]

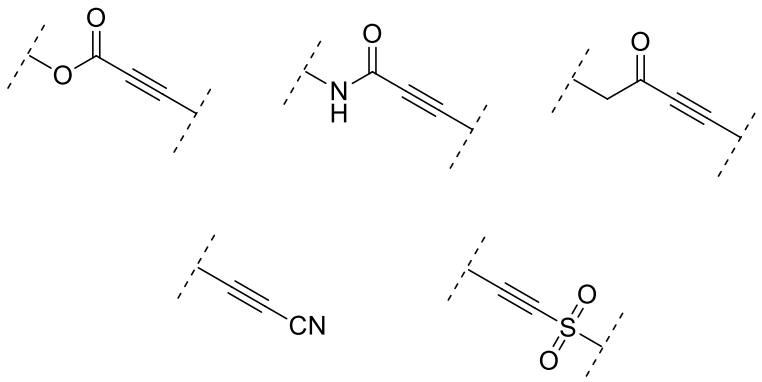
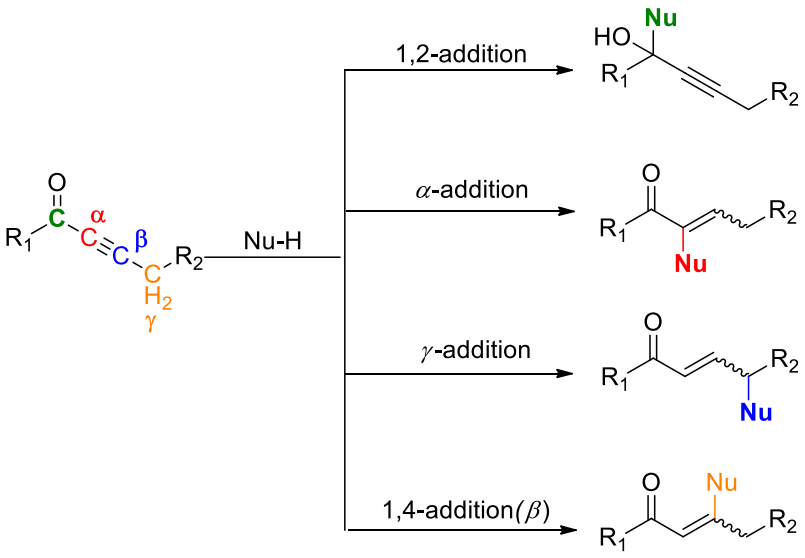


Fig 2.1. Commonly used activated alkynes.

2.2 General reactivity of activated alkynes

The most employed reaction with activated alkyne is the 1,4-addition due to superior reaction efficacy and the general ubiquity of heteroatoms in the products. 1,4-addition reaction plays a significant role in the introduction of new heteroatom functionalities such as thiol, amines etc. in an organic molecule for bioorganic and medicinal chemistry applications. The electrophilicity of the activated alkyne is extensively utilized in various cycloadditions,

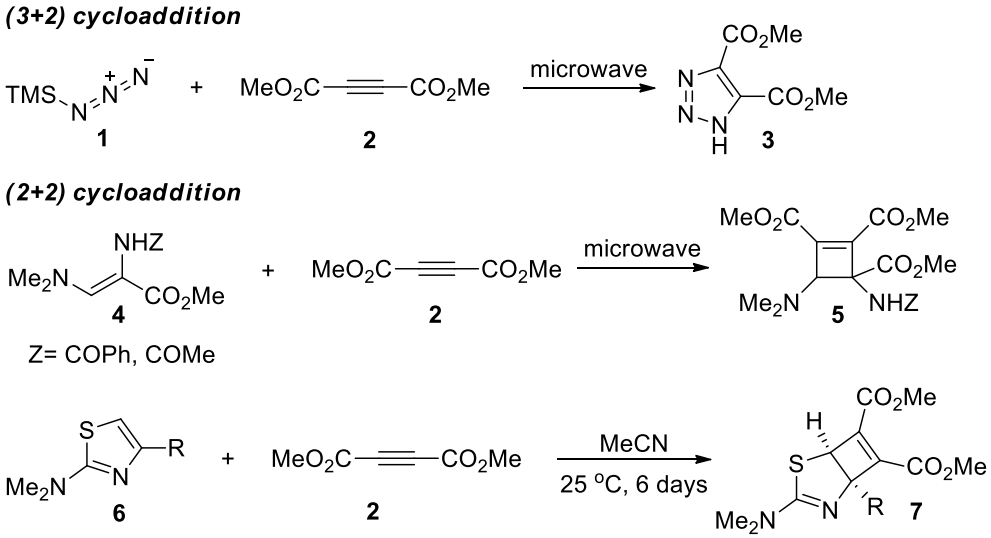
Michael additions and multicomponent reactions for the synthesis of different classes of molecules with wide range of applications.

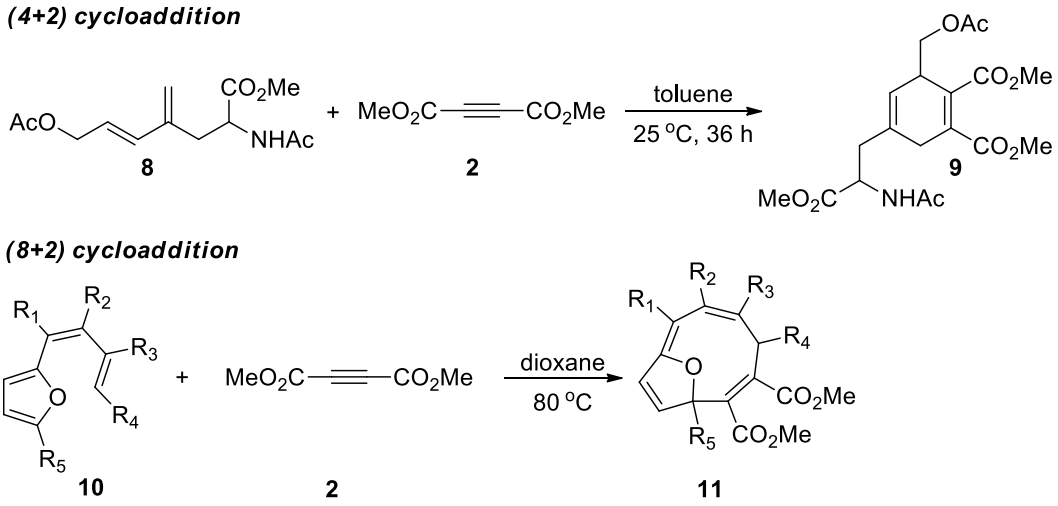


Scheme 2.1

2.2.1 Cycloaddition reactions

Activated alkynes are versatile dienophiles which are widely used in cycloaddition reactions. The most important example of cycloaddition is the Diels–Alder, in which very often dimethyl acetylenedicarboxylate (DMAD) is used as a standard for checking the efficiency of various dienes. DMAD is also a well explored dipolarophile in 1,3-dipolar cycloaddition reactions, [2+2], [8+2], [6+2] cycloadditions etc. (scheme 2.2).[2,3]

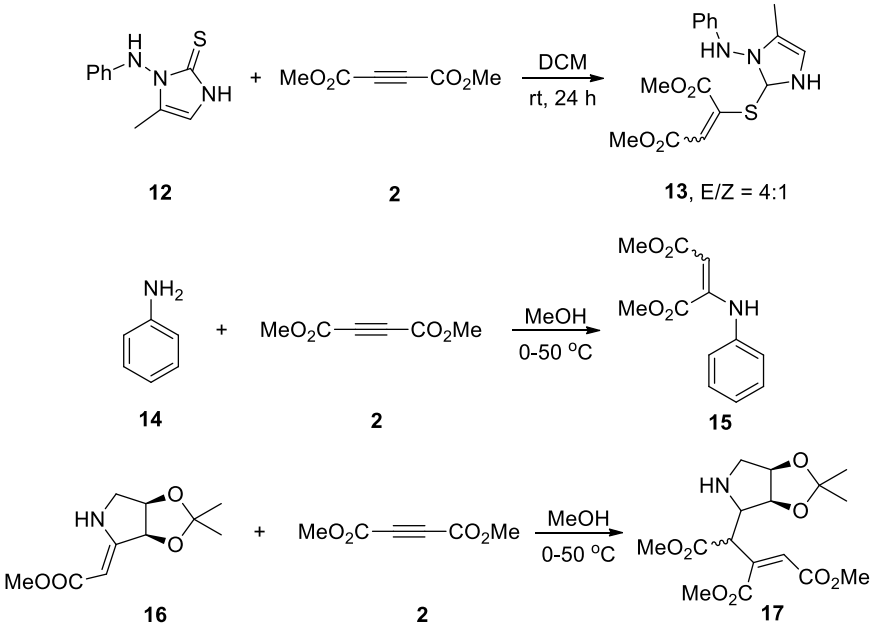




Scheme 2.2

2.2.2 Michael addition reactions

Activated alkynes are considered as good Michael acceptors due to an electron withdrawing group conjugated to the carbon-carbon triple bond. A variety of nucleophiles having nitrogen, sulphur and oxygen containing functional groups can act as Michael donors with activated alkynes (scheme 2.3).[1,2,3]

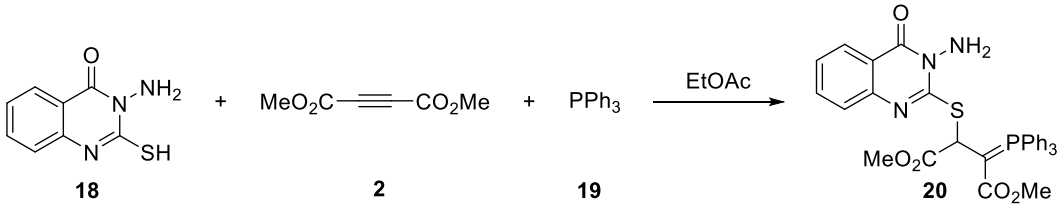


Scheme 2.3

The reactivity of activated alkynes strongly relies upon several aspects including, the electrophilicity of the activated alkyne, the strength of the nucleophile, solvent polarity, and the nature of the catalytic species.

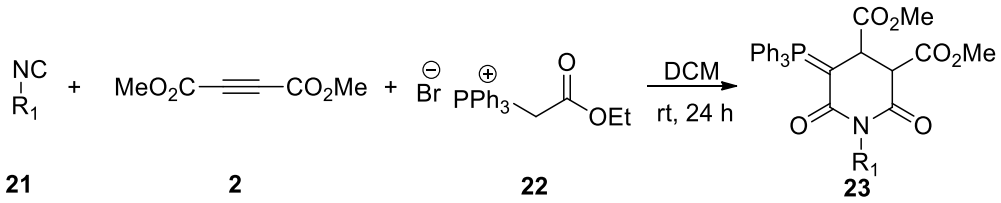
2.2.3 Multicomponent reactions (MCR) involving zwitterions

Zwitterions are intermediates which are formed transiently in the reaction between a neutral nucleophile and electrophilic receptors. In the case of DMAD, it can provide electron deficient site to an upcoming nucleophile. Khabazzadeha and coworkers demonstrated that DMAD reacted with N-H or S-H acids, such as 2-amino-4-phenylthiazole, 2-amino-5-(3-chloro-benzyl)thiazole, 3-amino-2-methylquinazolin-4-one and 3-amino-2- mercaptoquinazolin-4-one in the presence of triphenylphosphine to give phosphonium ylides *via* zwitterion formation (scheme 2.4). [4]



Scheme 2.4

Shaabani *et al.* reported a similar reaction of DMAD with an isocyanide and triphenylphosphonium bromide to give *N*-alkyl-2-triphenylphosphoranylidene glutarimides in one-pot without any catalyst (scheme 2.5).[5]

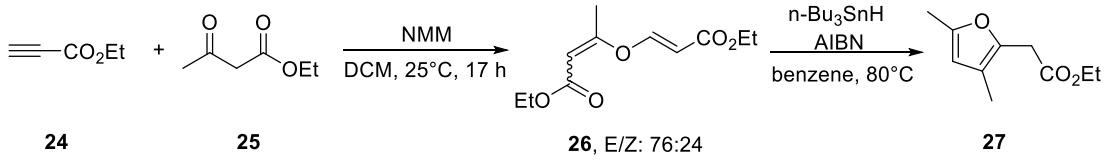


Scheme 2.5

2.2.4 Reactions of 1, 3-dicarbonyl compounds with activated alkynes

Activated alkynes with 1,3-dicarbonyl compounds are reported to have Michael addition, Michael addition followed by intramolecular cyclisation and multicomponent reactions.

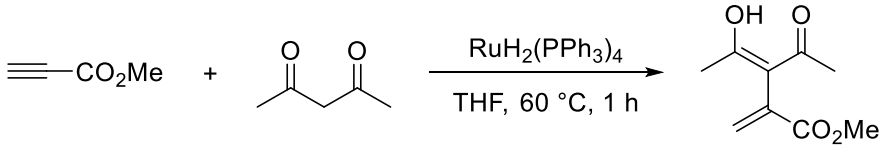
In 2003, Tae reported the synthesis of 2,3,5-trisubstituted furans under radical cyclization conditions (scheme 2.6). The reaction initiated with an unusual *O*-conjugate addition of *β*-ketoesters or 1,3-diketones with ethyl propionate in the presence of *N*-methyl morpholine. The divinyl ether compounds obtained under radical cyclization conditions gave substituted furans.[6]



24 **25** **26**, E/Z: 76:24 **27**

Scheme 2.6

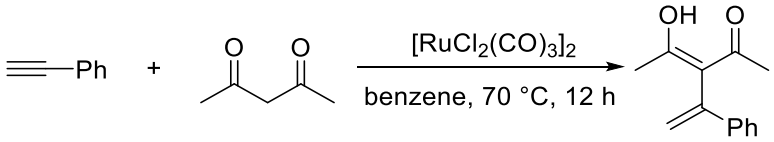
In 2009, Murahashi and coworkers reported a ruthenium catalyzed reaction of 1,3-diketones with terminal alkynes (scheme 2.7). Various 1,3-dicarbonyl compounds such as 1,3-diketones, *β*-keto esters, and *β*-keto amides underwent the reaction with various alkynes at the *α*-positions selectively. The reaction proceeded *via* insertion of ruthenium to the *α*-C–H bond of 1,3-dicarbonyl compounds which gave a ruthenium hydride intermediate, which upon insertion with the alkynes and subsequent reductive elimination of the ruthenium species afforded the Michael adduct.[7]



28 **29** **30**

Scheme 2.7

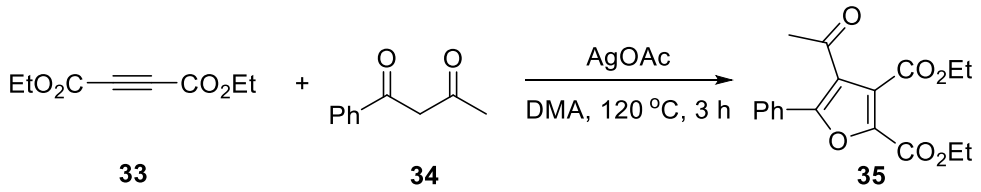
Later, Ryu *et. al.* explored another regiospecific ruthenium catalysed addition of 1,3-diketones to unactivated terminal alkynes in the presence of $[RuCl_2(CO)_3]_2$ catalyst (scheme 2.8).[8]



31 **29** **32**

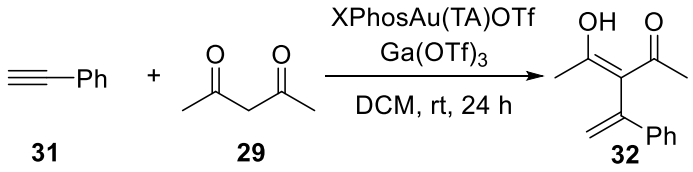
Scheme 2.8

A strategy involving a Michael addition followed by an oxidative cyclization of alkynoates with 1,3-dicarbonyl compounds under silver catalysis was reported by Zhang *et al.* in 2011. The reaction proceeds through a radical pathway and AgOAc plays a dual role as catalyst and also as the oxidant (scheme 2.9).[9]



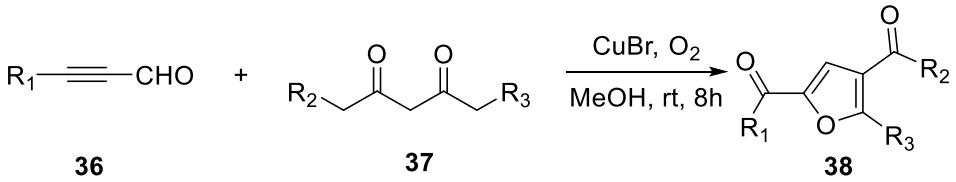
Scheme 2.9

The first cooperative gold/gallium catalysis for an intermolecular reaction between 1,3-dicarbonyl compounds and unactivated alkynes at room temperature was reported by Shi and coworkers in 2013. The reported Au/Ga system provided a new practical approach to achieve a highly active catalytic system for alkyne activation with low Au loading (scheme 2.10).[10]



Scheme 2.10

In 2013, Jiang and coworkers reported a one-pot Cu(I)-catalyzed reaction for the synthesis of 2-carbonyl furans *via* (2-furyl) carbene complexes. It is the first example of the regioselective synthesis of 2-carbonyl furans from an enyne-carbonyl compound *via* copper carbene oxidation. The reaction involved a Michael addition, Cu(I) mediated intramolecular *endo-dig* cyclization followed by air oxidation (scheme 2.11).[11]



Scheme 2.11

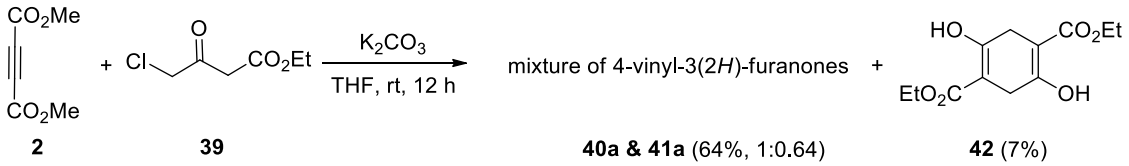
2.3 Statement of the problem

3(2*H*)-furanones are versatile oxygen containing derivatives of furans with a range of biological properties. The synthesis of such privileged scaffolds from readily available starting materials is highly desirable and a challenging task to organic chemists. Different synthetic protocols for the generation of such moieties were reported in literature, and the recent attraction is reactions involving 4-halo-1, 3-dicarbonyl compounds. In addition, literature suggested that the activated alkynes are considered as best Michael acceptors due to the inherent electrophilicity associated with the carbon-carbon triple bond in conjugation with the

electron withdrawing group. Hence, we planned to utilize the Michael acceptor character of activated alkynes with carbon nucleophile generated from 4-halo-1,3-dicarbonyl compounds. In this chapter we describe our efforts on the development of a base catalyzed tandem reaction for the synthesis of 4-vinyl-3(2*H*)-furanones from simple and easily available starting materials such as 4-halo-1, 3-dicarbonyl compounds and activated alkynes. The reaction takes places *via* tandem Michael addition-intramolecular cyclization pathway. The structural characterization of the products, detailed optimization studies and the generality of the reaction in terms of differently substituted activated alkynes and 4-halo-1, 3-dicarbonyl compounds is presented below.

2.4 Results and Discussion

We initiated the investigations with dimethyl acetylenedicarboxylate **2** and ethyl-4-chloroacetoacetate **39** as substrates (Scheme 2.12). The first reaction of **2** with **39** was performed in the presence of 2.0 equivalents of K_2CO_3 in THF at room temperature for 12 hours. From the reaction mixture, we isolated a mixture of 4-vinyl-3-(2*H*)-furanones in 64% yield. In addition, a dimer of ethyl-4-chloroacetoacetate, **42** was also isolated in 7% yield.



Scheme 2.12

The structure of **40a** and **41a** was assigned based on ^{1}H NMR, ^{13}C NMR and high-resolution mass spectral analyses. In the ^{1}H NMR spectrum (Fig 2.2) the two sets of signals corresponding to each proton confirmed the presence of two isomers. The vinylic protons resonated at 6.88 and 6.83 ppm respectively. The C2 methylene protons resonated at 4.68 and 4.66 ppm respectively. In the ^{13}C NMR spectrum (Fig 2.3) the furanone carbonyl resonated at 192.0 and 191.9 ppm and the C5 carbons resonated at 180.6 and 180.3 ppm respectively. The alkene carbons resonated at 137.6, 137.0, 113.4 and 112.5 ppm and the C2 methylene carbons resonated at 75.3 and 75.2 ppm respectively. All other signals in the ^{1}H and ^{13}C NMR spectra were in agreement with the proposed structure. The high resolution mass spectral analysis showed a peak at *m/z* 293.0626 $(M+Na)^+$, which also supported the proposed structure.

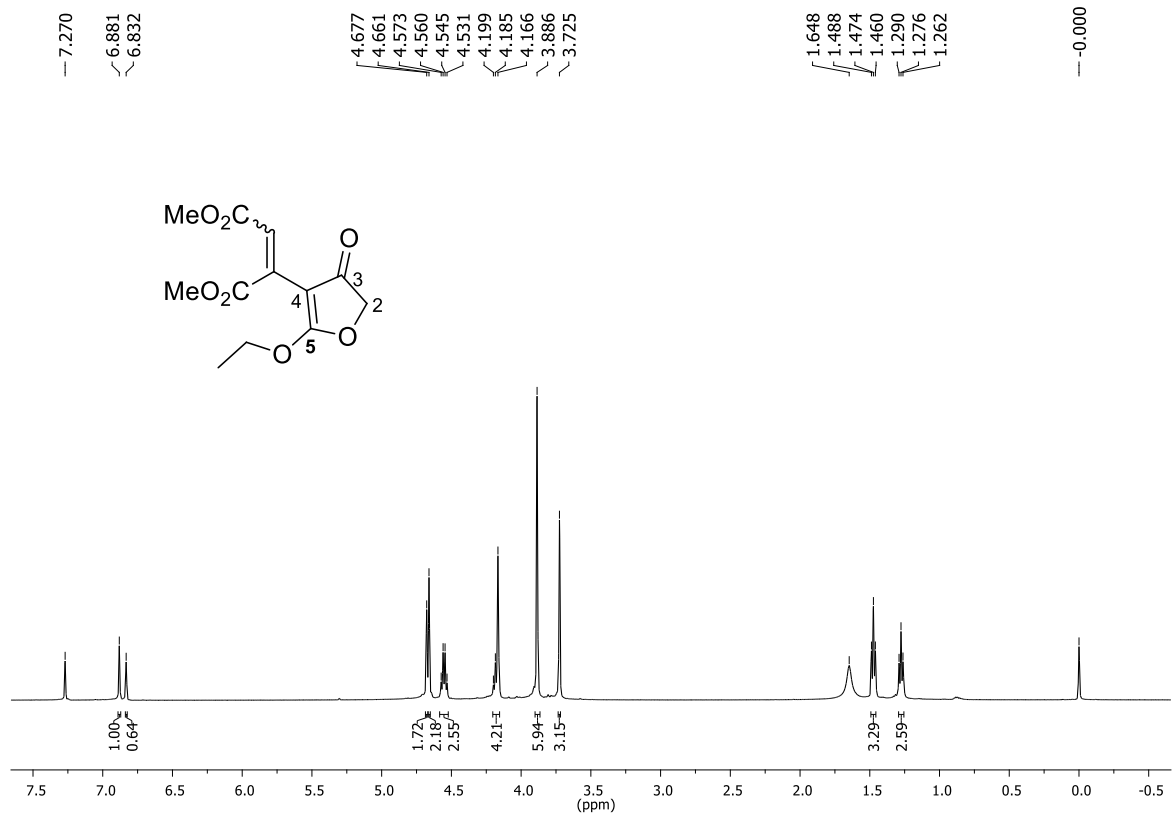


Fig 2.2. ^{1}H NMR of compound **40a**/**41a**.

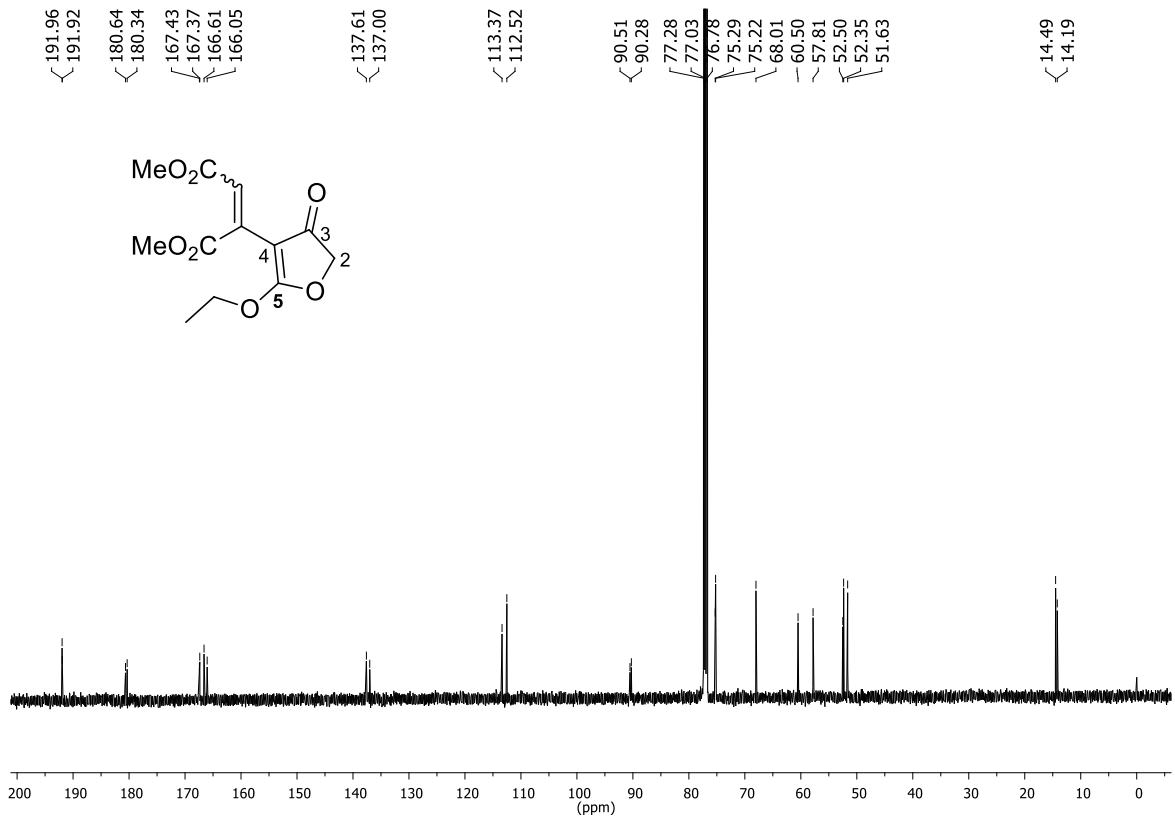
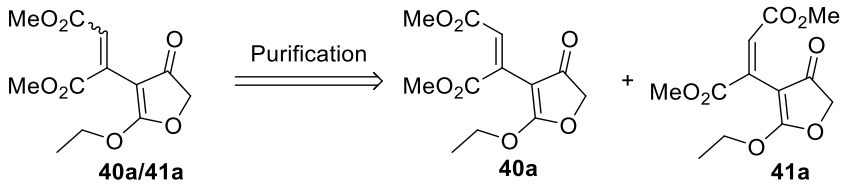


Fig 2.3. ^{13}C NMR of compound **40a**/**41a**.

Our next effort was to isolate the isomers in order to confirm the structures and in this line, we carried out an additional column chromatography which took us 3 days to separate between the two (Scheme 2.13).



Scheme 2.13

Then we compared the ^{1}H NMR spectra (Fig 2.4) of the isolated isomers and both the isomers showed the presence of alkene proton, furanone methylene, ethoxy methylene and two methoxy groups. We have observed some significant differences in the chemical shift values of the methylene protons (1') in the ethoxy group of two isomers. In the first isomer, it resonated at 4.6 ppm while in the second case it was seen at 4.1 ppm. Other protons also showed significant differences in the ^{1}H NMR values. In the ^{13}C NMR also differences were observed in the range 50-70 ppm (Fig 2.5). And these observations suggested the fact that the isomers are not *E*/*Z* isomers as expected.

In the HMBC spectra of first isomer **40a** (Fig 2.6), the methylene proton in the ethoxy group showed correlations with C5 carbon of the furanone, which confirmed the connectivity of ethoxy group at the C5 position of furanone. While in the second case **41a** (Fig 2.7), the methoxy protons showed HMBC correlation with C5 carbon and the ethoxy group showed correlation with ester carbonyl of activated alkyne part (Scheme 2.14). From the HMBC studies, it is clear that the isomers formed are not *E*/*Z* isomers of vinylfuranones. The HMBC correlations are marked in red in the scheme.

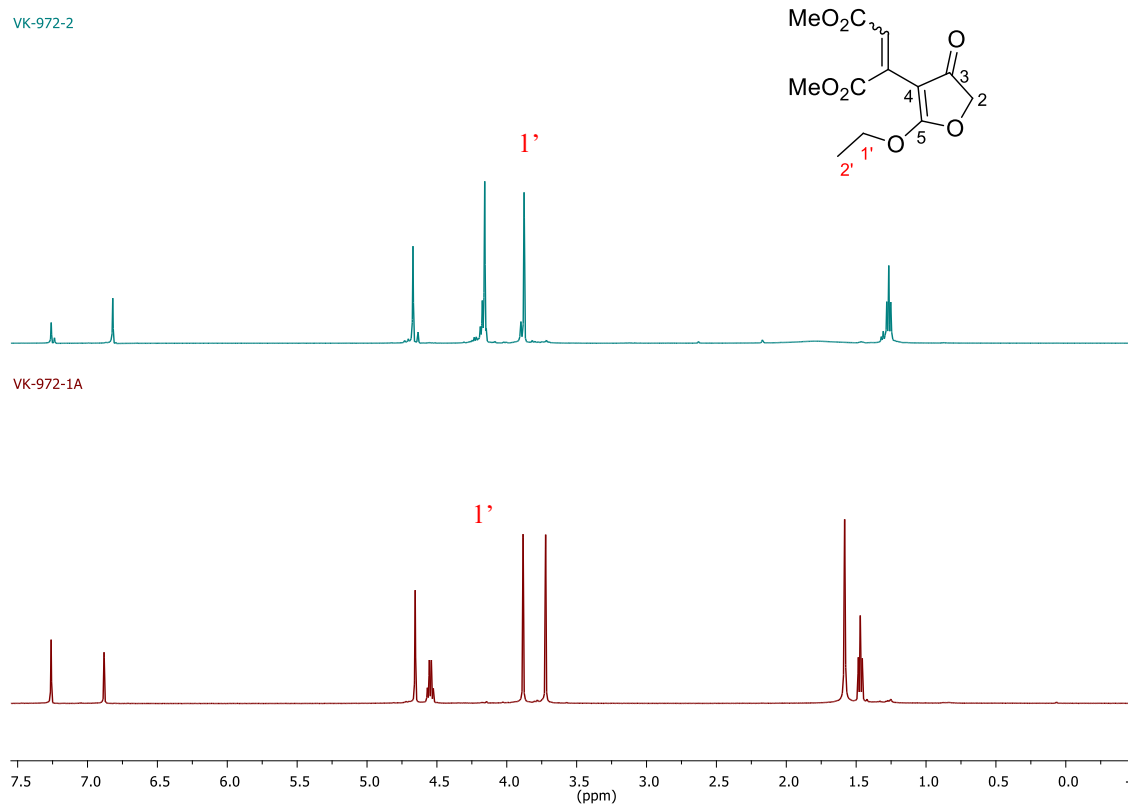


Fig 2.4. Comparison of ^{1}H NMR of compound **40a**/**41a**.

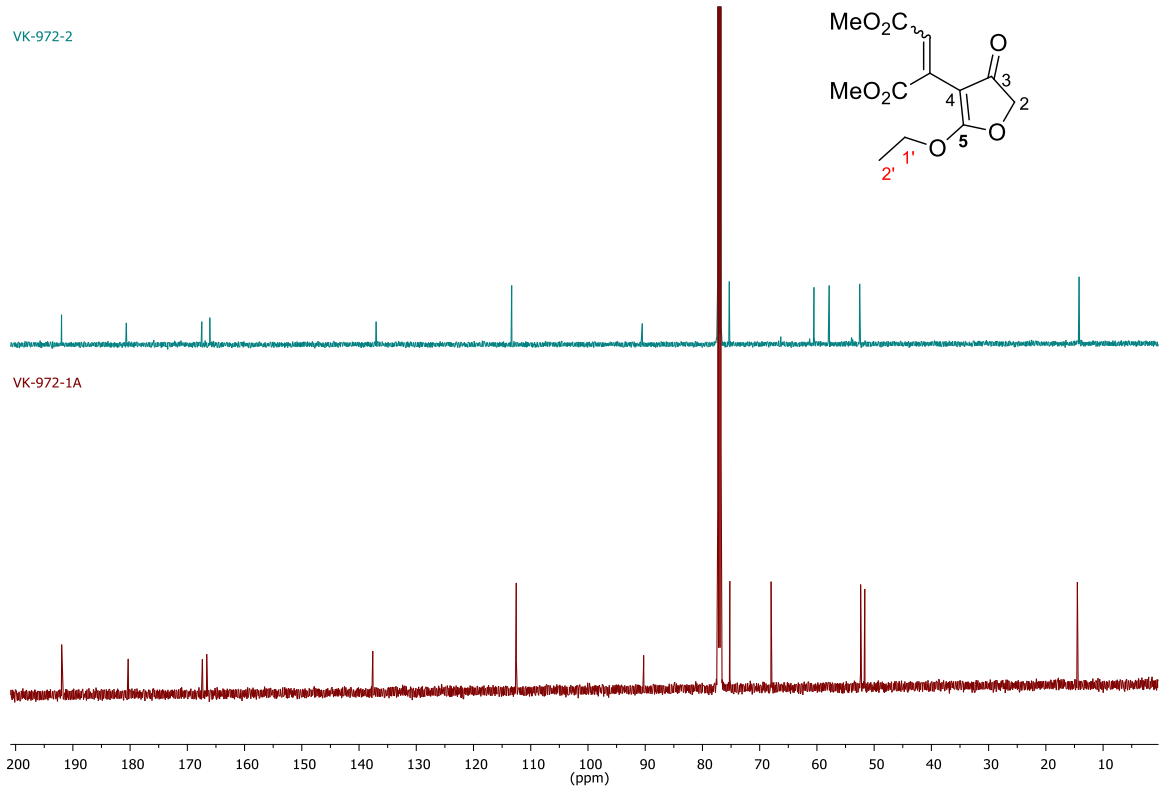


Fig 2.5. Comparison of ^{13}C NMR of compound **40a**/**41a**.

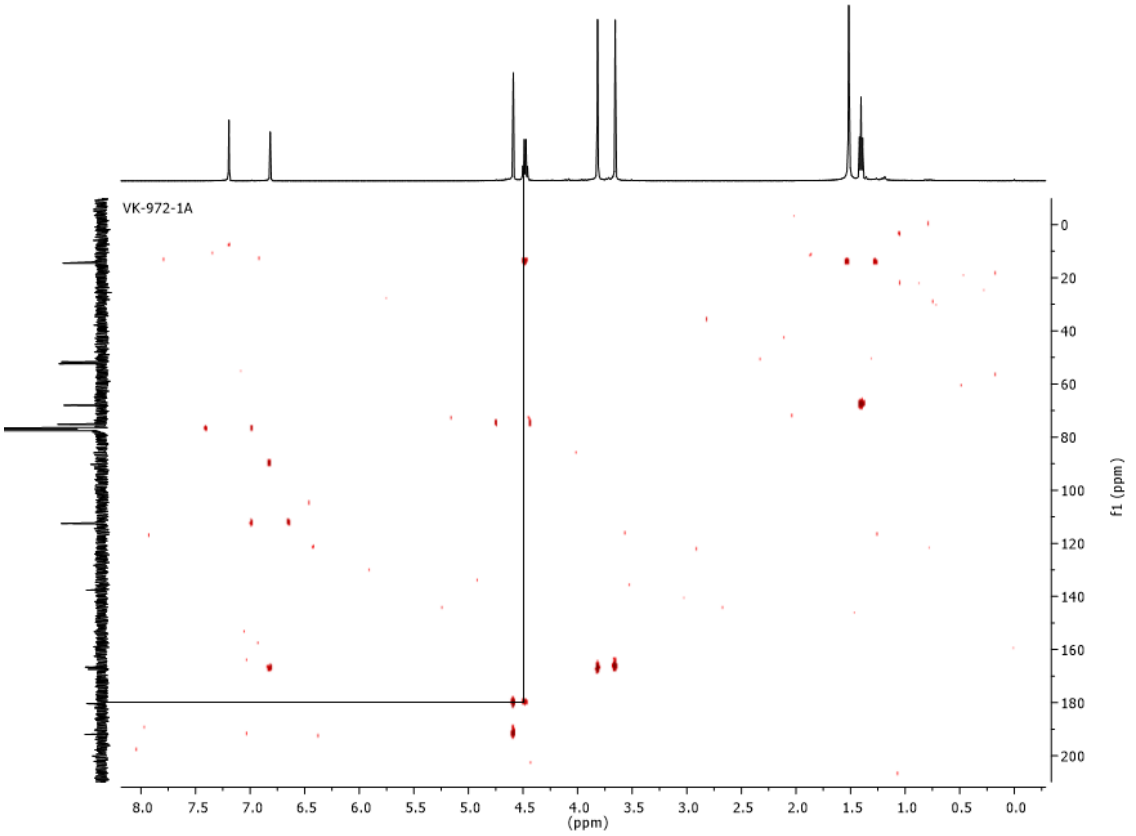


Fig 2.6. HMBC of compound **40a**.

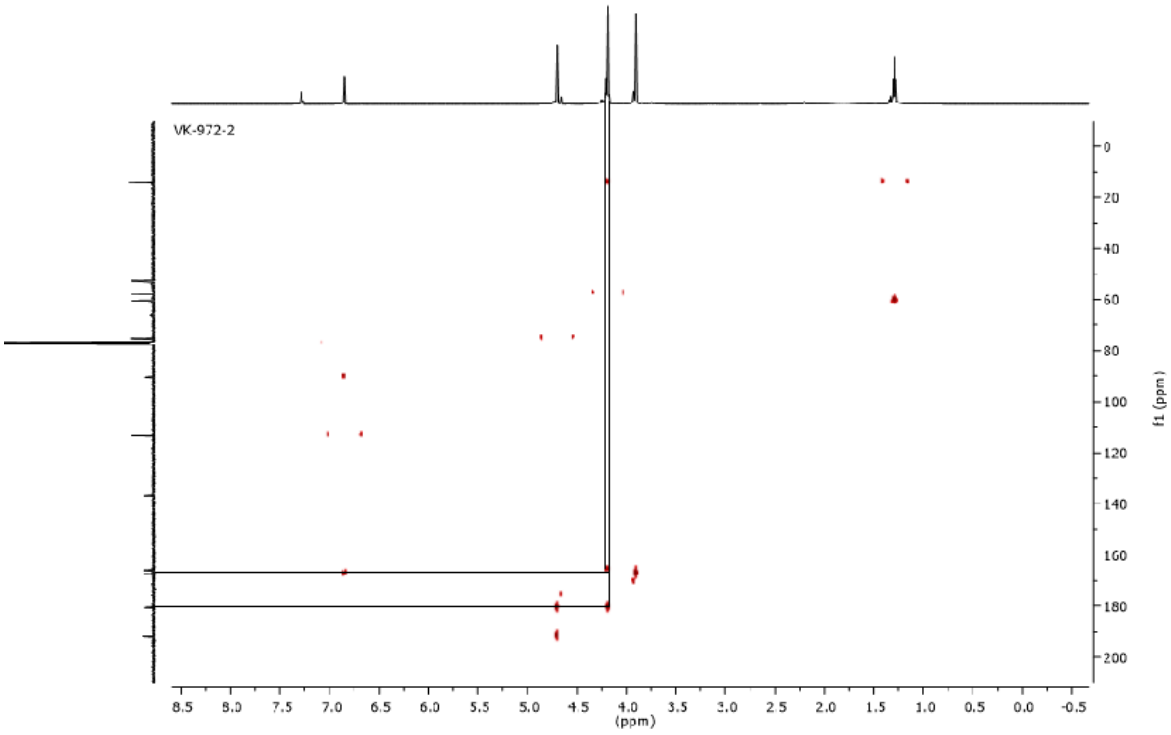
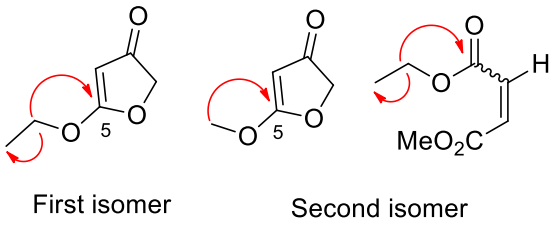


Fig 2.7. HMBC of compound **41a**.



Scheme 2.14

For further confirmation of the data obtained from NMR analyses, we crystallized both products and performed single crystal X-ray analyses. The first isomer was crystallised using DCM/Hexane solvent system while the second as crystallised from DCM/cyclohexane system. The single crystal X-ray structures of **40a** and **41a** are shown in figure 2.8. From the crystal data, it is evident that the structure of **40a** was as expected. In the crystal structure of **41a**, we observed that an interchange between the alkyl groups of the ester moieties of **2** and **39** had taken place and hence a regioisomer of **41a**.

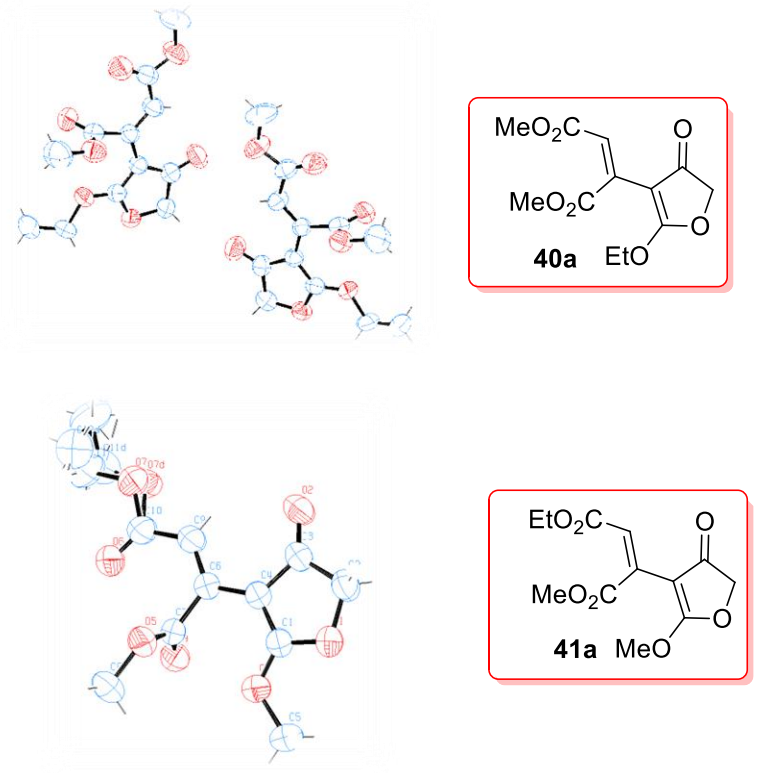
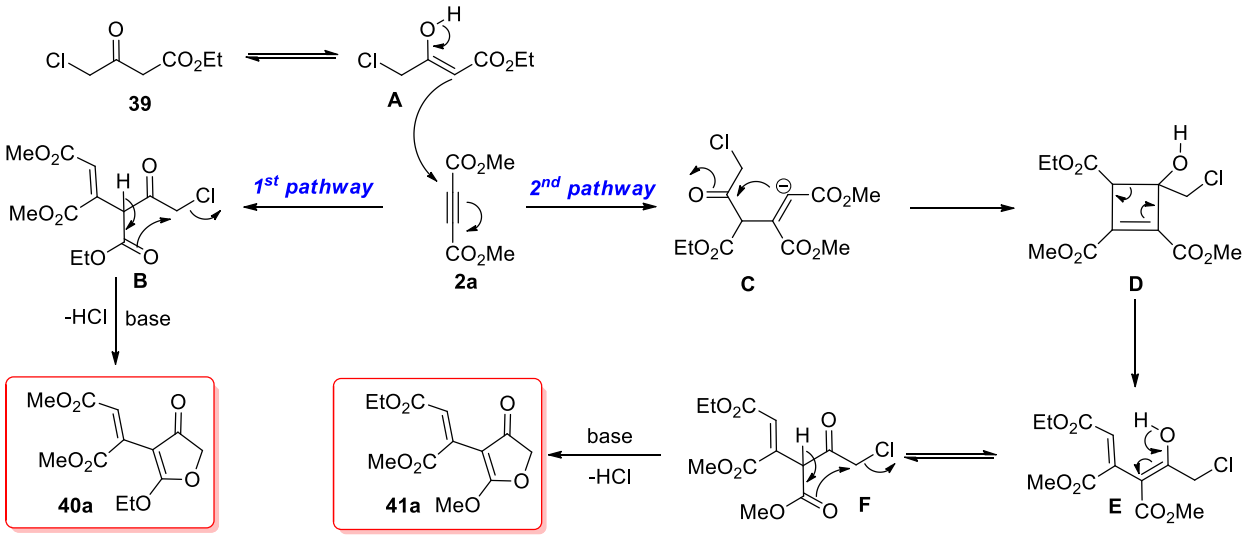


Fig 2.8. Single crystal X-ray of **40a** (CCDC: 2179228) & **41a** (CCDC: 2179229).

The possible mechanisms for the formation of both **40a** and the regioisomer **41a** are depicted in scheme 2.15. Both the pathways start with the Michael addition of **39** to **2**. Keto-enol tautomerism is possible in ethyl-4-chloroacetoacate **39** and the enol form **A** undergoes a Michael addition with the activated alkyne to form **B**. Then, base abstracts the acidic proton in

intermediate **B** generating the ester enolate which then attacks (*via* enolate oxygen) the carbon bearing the halogen furnishing the expected 4-vinyl-3-(2*H*)-furanone **40a**. Stepwise [2+2] cycloadditions of enamines and enols to activated alkynes towards cyclobutenes is well explored and the 2nd pathway is proposed based on these literature precedents.[12,13,14] The 2nd pathway starts with the attack of the vinylic anionic centre to the carbonyl carbon forming the cyclobutene intermediate **D**. A 4π-ring opening takes place in **D** furnishing the diene **E** which upon tautomerization affords intermediate **F**. Finally, as seen in the previous pathway, base abstracts the acidic proton in intermediate **F** generating the ester enolate which then attacks (*via* enolate oxygen) the carbon bearing the halogen furnishing the unexpected regioisomer 4-vinyl-3-(2*H*)-furanone **41a**.

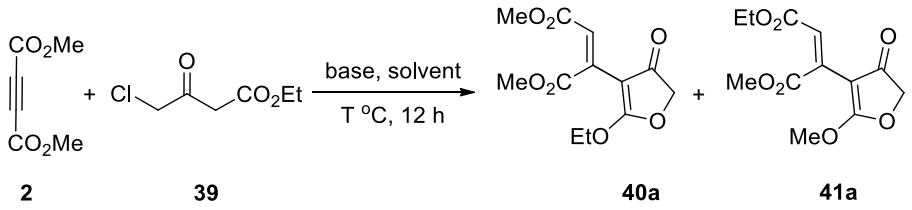


Scheme 2.15

Our next focus was on finding the best conditions for achieving the highest yield for 4-vinyl-3-(2*H*)-furanones with **39** and **2** as model substrates (Table 2.1). The optimization studies commenced with the screening of bases such as Na_2CO_3, K_2CO_3, NaOAc, Et_3N, CsOAc and NH_4OAc. (Table 2.1, entries 1- 6). Among the screened bases, Na_2CO_3 gave the maximum yield of 82% for the mixture of **40a** and **41a**. Next, we examined different solvents such as THF, CH_3CN, DMF and toluene. From the solvent optimization, our initial choice of THF was found to be the best medium for the present transformation (Table 2.1, entries 7-9). Increasing the temperature and time of the reaction did not have any marked improvements in the outcome. Thus, the optimized conditions for the reaction was found to be a combination of 1.0 equivalent of activated alkyne **2**, 1.1 equivalent of 4-haloacetoacetate **39** and 2.0 equivalents of Na_2CO_3

as base in THF at room temperature for 12 h. In all cases, we isolated the mixture of **40a** and **41a**.

Table 2.1. Optimization studies



2 **39** **40a** **41a**

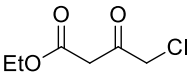
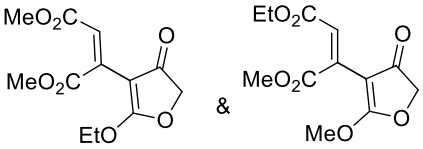
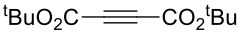
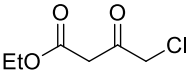
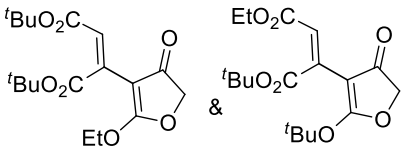
Entry	Base	Solvent	Yield of **40a** & **41a** (%)[a]
1	K_2CO_3	THF	64
2	**Na_2CO_3**	**THF**	**82**
3	NaOAc	THF	75
4	Et_3N	THF	44
5	CsOAc	THF	41
6	NH_4OAc	THF	-
7	Na_2CO_3	CH_3CN	40
8	Na_2CO_3	toluene	45
9	Na_2CO_3	DMF	35
10[b]	Na_2CO_3	THF	43
11[c]	Na_2CO_3	THF	80

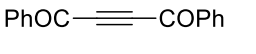
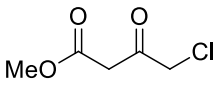
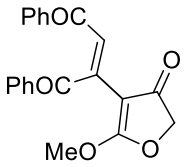
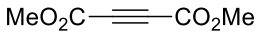
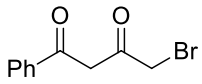
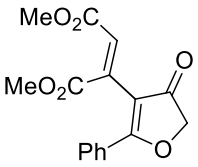
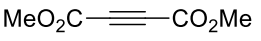
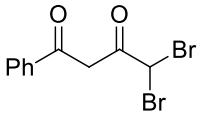
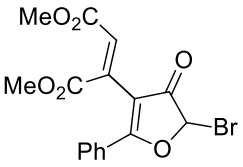
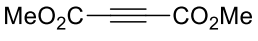
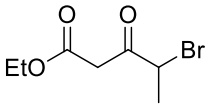
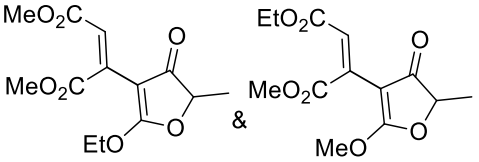
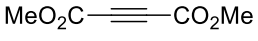
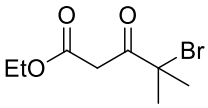
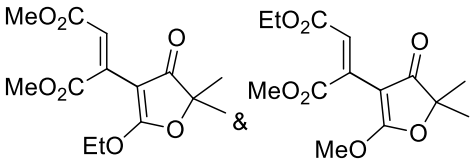
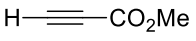
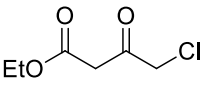
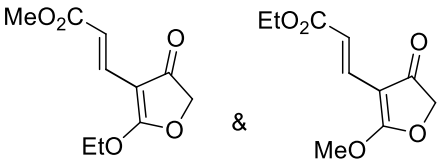
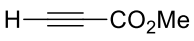
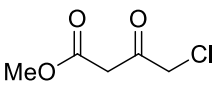
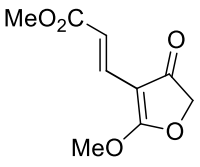
Reaction conditions: [a] **2** (1.0 equiv., 0.70 mmol), **39** (1.1 equiv., 0.78 mmol), base (2.0 equiv.), solvent (4.0 mL), rt, 12 h, isolated yield; [b] 50 °C; [c] 24 h.

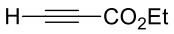
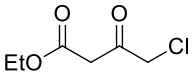
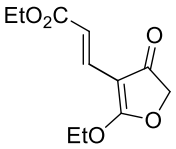
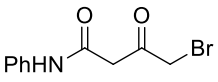
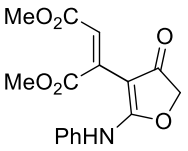
The optimized conditions for the tandem Michael addition/intramolecular cyclisation strategy were initially utilized for studying the generality of differently substituted activated alkynes (Table 2.2). The reaction of dimethylacetylenedicarboxylate **2** and ethyl-4-chloroacetoacetate **39** under the optimized condition afforded a 1:0.69 mixture of 4-vinyl-3(2*H*)-furanones **40a** and the regioisomer **41a** in 82% yield. In a similar fashion, di-*tert*-butyl acetylenedicarboxylate **2b** also reacted with **39** furnishing a 1:0.62 regioisomeric mixture of 4-

vinyl-3(2*H*)-furanones **40b** and **41b** in 39% yield. The reaction of 1,4-diphenylbut-2-yne-1,4-dione **2c** with methyl-4-chloroacetoacetate **39f** furnished only the 4-vinyl-3(2*H*)-furanones **40c** due to the presence of the keto-group instead of the ester moiety thereby preventing the 2nd pathway towards the stepwise [2+2] cycloaddition and subsequent electrocyclic 4π-ring opening. The reactions of 4-bromo-1-phenylbutane-1,3-dione **39b** and 4,4-dibromo-1-phenylbutane-1,3-dione **39c** with dimethylacetylenedicarboxylate **2** also resulted in 4-vinyl-3(2*H*)-furanones **40d** and **40e** (Table 2.2). It is noteworthy to mention that in **40e** (despite of the poor yield), a bromine functionality could be placed at the 2nd position by starting from 2,4-dibromo-1-phenylbutane-1,3-dione **39c**. The same strategy was adopted for introducing methyl substituents at the 2nd position of 3(2*H*)-furanone ring by carrying out reactions of ethyl 4-bromo-3-oxopentanoate **39d** and ethyl 4-bromo-4-methyl-3-oxopentanoate **39e** with dimethylacetylenedicarboxylate **2**. These reactions also afforded regioisomeric mixtures of furanones (**40f** & **41f** and **40g** & **41g**) in satisfactory yields. The reaction of methyl propiolate **2d** with ethyl-4-chloroacetoacetate **39** yielded a 1:0.2 regioisomeric mixture of 4-vinyl-3(2*H*)-furanones **40h** and **41h** in 42% yield. Finally, the reactions of methyl propiolate **2d** with methyl-4-chloroacetoacetate **39f** and ethyl propiolate **2e** with ethyl-4-chloroacetoacetate **39** afforded corresponding 4-vinyl-3(2*H*)-furanones **40i** and **40j** in 55% and 48% yields respectively.

Table 2.2. Generality of 4-vinyl-3-(2*H*)-furanone synthesis with various activated alkynes

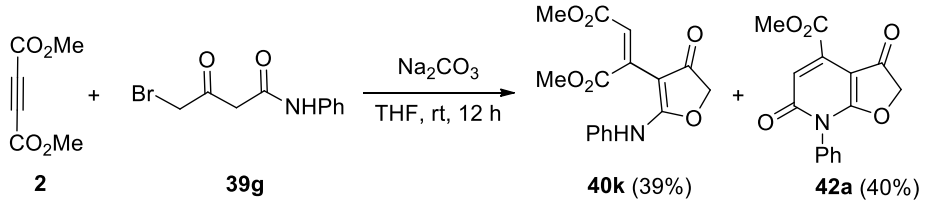
Entry	Acetylene	4-Halo-1,3-dicarbonyl compound	Product	Yield (%)
1	 **2**	 **39**	 **40a** & **41a** (1: 0.69)	82
2	 **2b**	 **39**	 **40b** & **41b** (1: 0.62)	39

3	 **2c**	 **39f**	 **40c**	30
4	 **2**	 **39b**	 **40d**	51
5	 **2**	 **39c**	 **40e**	11
6	 **2**	 **39d**	 **40f** & **41f** (1:0.29)	80
7	 **2**	 **39e**	 **40g** & **41g** (1:0.65)	57
8	 **2b**	 **39**	 **40h** & **41h** (1:0.20)	42
9	 **2d**	 **39f**	 **40i**	55

10	 **2e**	 **39**	 **40j**	48
11	 **2**	 **39g**	 **40k**	39

Reaction conditions: **2** (1.0 equiv.), **39** (1.1 equiv.), Na_2CO_3 (2.0 equiv.), THF, rt, 12 h

An interesting observation was made when 4-bromo-3-oxo-*N*-phenylbutanamide **39g** was allowed to react with dimethylacetylene dicarboxylate **2** (Scheme 2.16). Along with the expected 4-vinyl-3(2*H*)-furanone **40k**, a 3(2*H*)-furanone fused 2-pyridone **42a** was isolated in 40% yield. The structure of **42a** was assigned based on ^1H, ^{13}C NMR analyses and mass spectrometry.



2 **39g** **40k** (39%) **42a** (40%)

Scheme 2.16

In the ^1H NMR spectrum of **42a** (Fig 2.9**),** the aromatic protons were found to resonate between 7.23-7.51 ppm. The alkene proton resonated at 6.60 ppm. The C2 methylene protons resonated at 3.91 ppm. In the ^{13}C NMR spectrum (Fig 2.10**),** the furanone carbonyl carbon resonated at 187.3 ppm and the C5 carbons resonated at 174.5 ppm. The ester and amide carbonyls resonated at 163.9 and 161.8 ppm respectively. All other signals in the ^1H and ^{13}C NMR spectra were in agreement with the proposed structure. The high resolution mass spectral analysis showed a peak at *m/z* 308.0533 $(M+Na)^+$, which also supported the proposed structure.

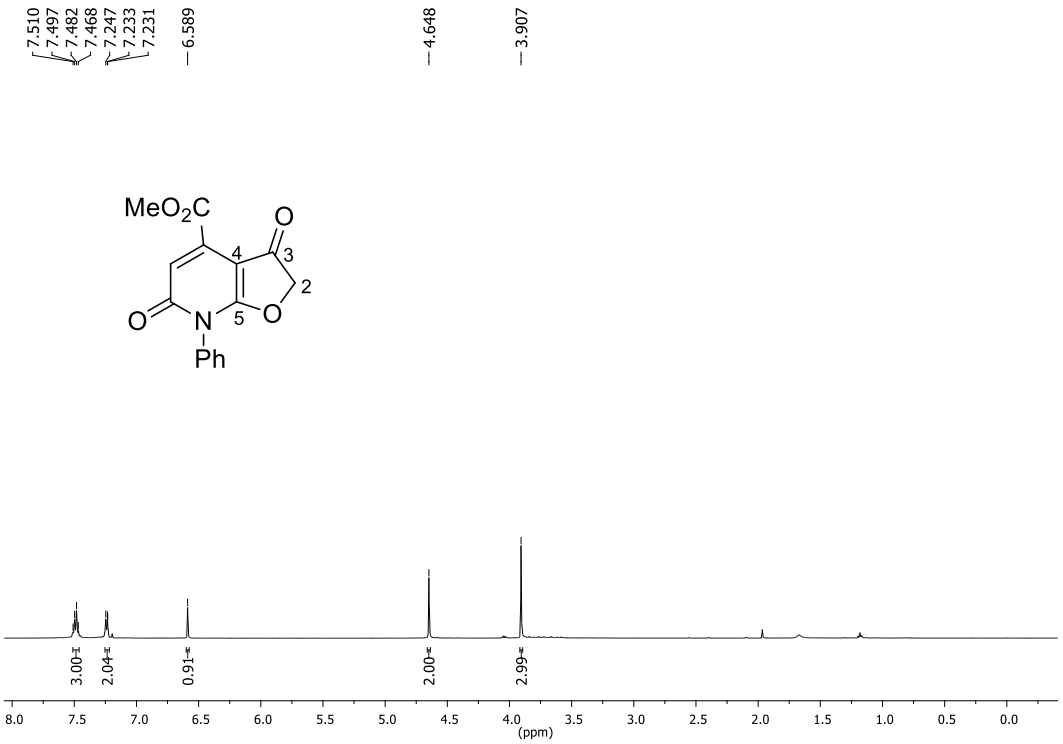


Fig 2.9. [1]H NMR of compound **42a**.

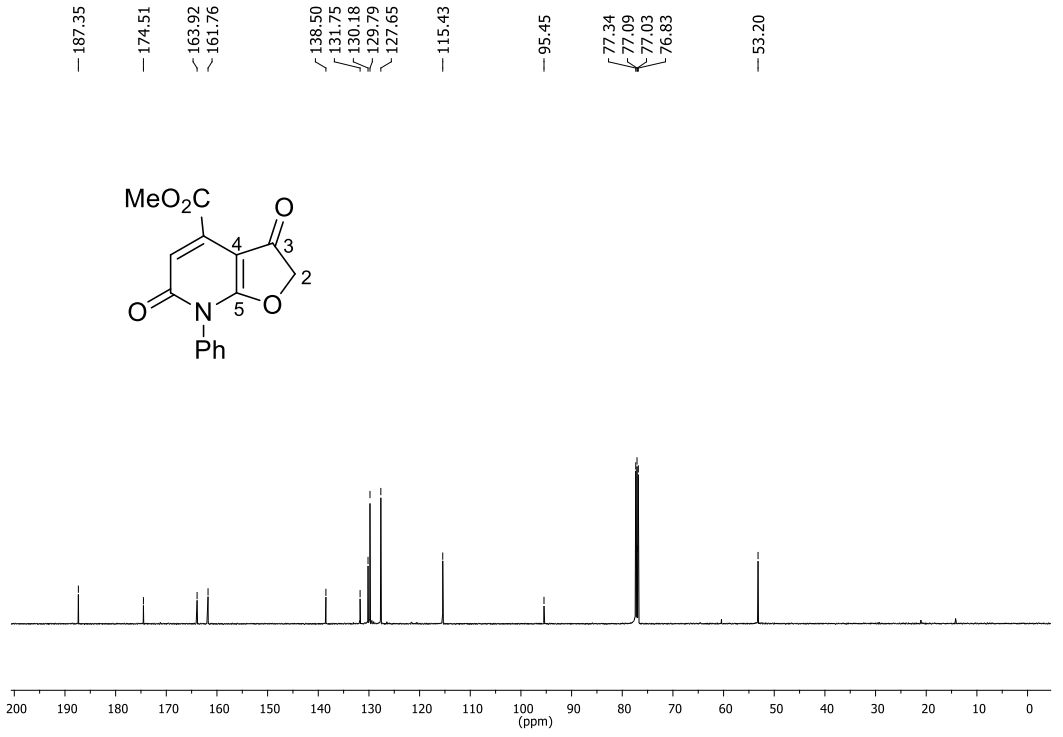
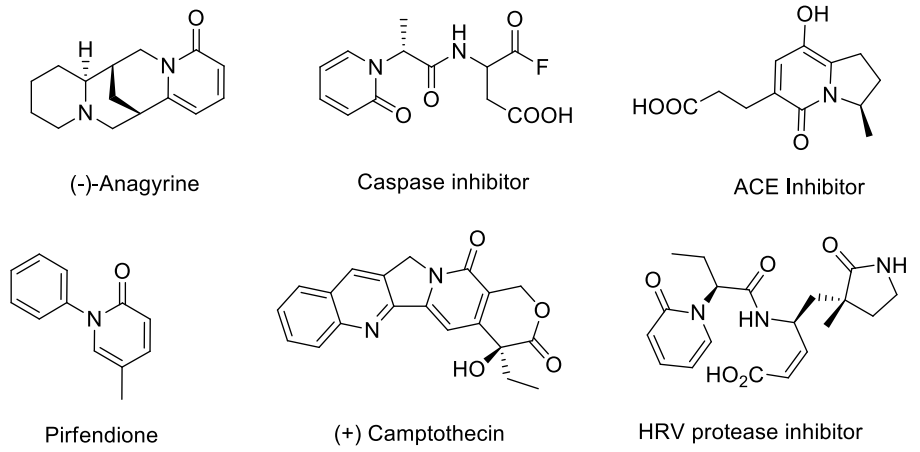


Fig 2.10: [13] C NMR of compound **42a**.

2-Pyridone is considered as a privileged pharmacophore in medicinal chemistry. It is widely found in natural products such as Camptothecin (antitumor), (−)-maximiscin (Tumour growth suppression), (+)-hosieine A (Nicotinic acetylcholine receptor ligand), (+)-lyconadin

A (cytotoxic to murine lymphoma L1210 cells and KB cells and Enhances mRNA expression for nerve growth factor in astrocytoma cells) and other bioactives like huperzine A (anti-Alzheimer), milrinone (anti-heart failure) and SD-560 (anti-fibrosis) (Scheme 2.17). The latest addition to this library is tazemetostat (TazverikTM), the first EZH_2 inhibitor approved by FDA 2020 for epithelioid sarcoma treatment (Fig 2.11).[15-18]

In literature, significant progress can be observed in the chemistry towards 2-pyridone, such as intrinsic electrophilic substitutions, pyridine hydrolysis, synthesis of the 2-pyridone ring from acyclic precursors and transition metal catalysis. Even though the literature is flooded with reports, the common disadvantages associated with these includes the requirement of specially functionalized substrates or harsh reaction conditions which significantly limit the scope. Therefore, development of general and efficient approaches for rapid synthesis of 2-pyridone derivatives from readily available starting materials is highly desirable and yet challenging.



Scheme 2.17

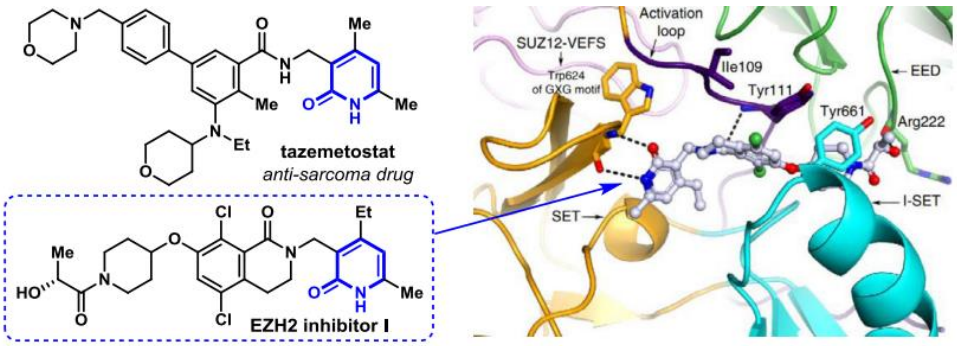
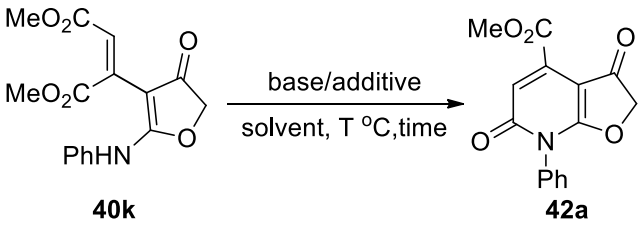


Fig 2.11. 2-pyridone containing EZH_2 inhibitor and its action.

On account of the biological importance of the 2-pyridone moiety and intrigued by the formation of this interesting 3(2*H*)-furanone fused pyridone scaffold, we became curious to

find suitable conditions to isolate it as the sole product. A detailed study was carried out for the exclusive synthesis of 3(2*H*)-furanone fused 2-pyrridone **42a** from 4-vinyl-3(2*H*)-furanone **40k** by using different bases, solvents, additives and by varying time and temperature (Table 2.3). We first checked the effect of the amount of base used in both reactions with 1.0 and 2.0 equivalents of Na_2CO_3 in THF resulted in incomplete conversions (Table 2.3, entries 1-2). The screening of bases such as K_2CO_3, K_3PO_4 and Cs_2CO_3 also gave a mixture of **40k** and **42a** whereas with KOH and KO^{t}Bu no reaction was observed (Table 2.3, entries 3-7). Heating the reaction to 50 ^oC in the presence of 2.0 equivalents of Na_2CO_3 also furnished an incomplete reaction. Then we added 10.0 equivalents of *p*-TSA as an additive and performed two reactions at rt and 50 ^oC; both of which failed to afford a complete conversion (Table 2.3, entries 9-10). In the meantime, we came across an acid mediated 2-pyridone synthesis and hence we tried reactions with 10.0 equivalents of AcOH at rt, 50 ^oC and 100 ^oC in ^{i}PrOH (Table 2.3, entries 11-13). The first two reactions gave a mixture of **40k** & **42a** whereas the reaction at 100 ^oC afforded the 3(2*H*)-furanone fused 2-pyrridone **42a** in 49% yield. Finally, the reaction with 10.0 equivalents of pivalic acid at 100 ^oC afforded the expected pyridone fused 3(2*H*)-furanone **42a** in 70% yield (Table 2.3, entry 14).

Table 2.3. Conversion of 4-vinyl-3-(2*H*)-furanone **40k** to 2-pyridone fused 3(2*H*)-furanone **42a**



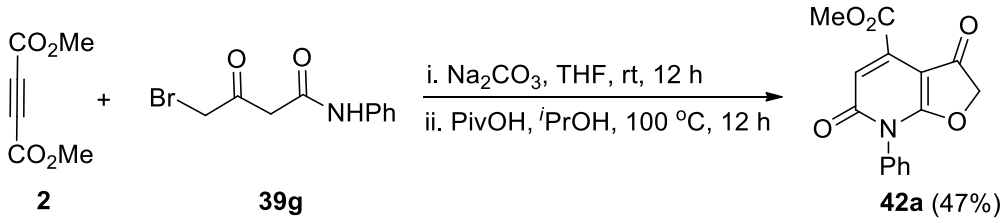
40k **42a**

Entry	Base/Additive	Solvent	Yield[a]
1	Na_2CO_3 (1.0 equiv.)	THF	Mixture of **40k** & **42a**
2	Na_2CO_3 (2.0 equiv.)	THF	Mixture of **40k** & **42a**
3	K_2CO_3 (1.0 equiv.)	THF	Mixture of **40k** & **42a**
4	K_3PO_4 (1.0 equiv.)	THF	Mixture of **40k** & **42a**
5	KOH (1.0 equiv.)	THF	NR
6	Cs_2CO_3 (1.0 equiv.)	THF	Mixture of **40k** & **42a**

7	KO^{t}Bu (1.0 equiv.)	THF	NR
8[b]	Na_2CO_3 (2.0 equiv.)	THF	Mixture of **40k** & **42a**
9	*p*TSA (10.0 equiv.)	THF	Mixture of **40k** & **42a**
10	*p*TSA (10.0 equiv.)	THF	Mixture of **40k** & **42a**
11	AcOH (10.0 equiv.)	^{i}PrOH	Mixture of **40k** & **42a**
12[b]	AcOH (10.0 equiv.)	^{i}PrOH	Mixture of **40k** & **42a**
13[c]	AcOH (10.0 equiv.)	^{i}PrOH	**42a** (49%)
14[c]	Pivalic acid (10.0 equiv.)	^{i}PrOH	**42a** (70%)

Reaction conditions: [a] **40k** (0.08 mmol), solvent (2.0 mL), rt, 12 h; [b] 50 ^{o}C, 12 h; [c] 100 ^{o}C, 12 h.

Our next attempt was to develop a one-pot process for synthesizing 3(2*H*)-furanone fused 2-pyrridone from 4-bromo-3-oxo-*N*-phenylbutanamide and an activated alkyne. First, 4-bromo-3-oxo-*N*-phenylbutanamide **39g** was allowed to react with dimethylacetylene dicarboxylate **2** under the optimized condition for the formation of 4-vinyl-3-(2*H*)-furanone (Scheme 2.31). After 12 h, the reaction mixture was evaporated and to the crude 10.0 equivalents of pivalic acid followed by ^{i}PrOH as solvent was added and the mixture was allowed to stir at 100 ^{o}C for 12 h. From this one-pot reaction, the 3(2*H*)-furanone fused 2-pyrridone **42a** was isolated in 47% yield.



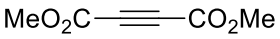
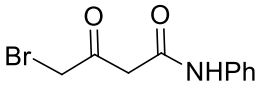
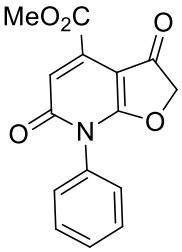
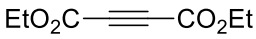
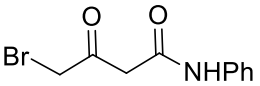
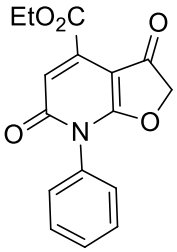
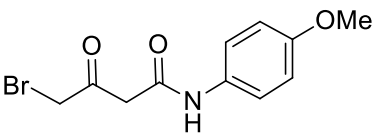
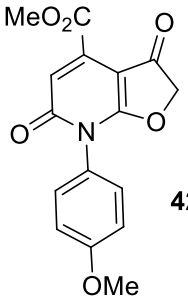
Scheme 2.31

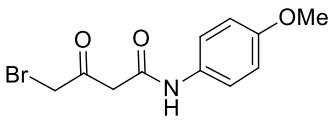
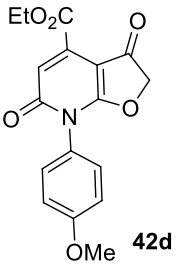
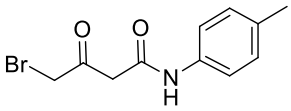
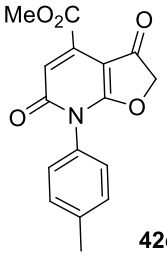
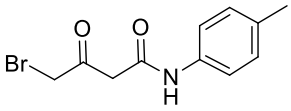
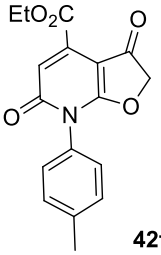
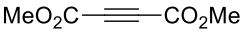
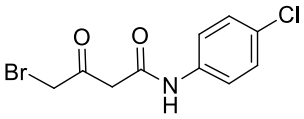
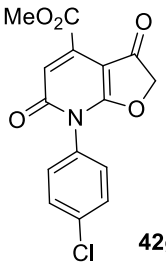
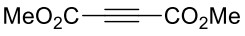
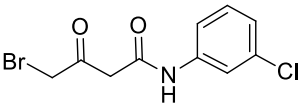
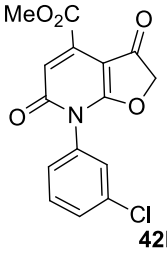
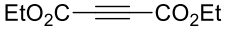
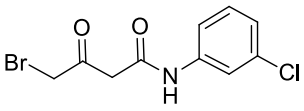
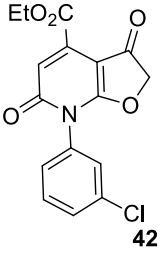
Having developed a one-pot method for the synthesis of 3(2*H*)-furanone fused 2-pyridone analogues, we proceeded by checking the generality with various substituted 4-bromo-3-oxo-*N*-aryl/alkyl-butanamides (Table 2.4).

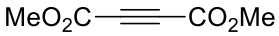
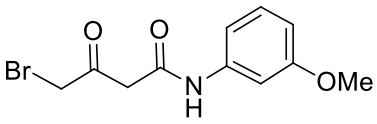
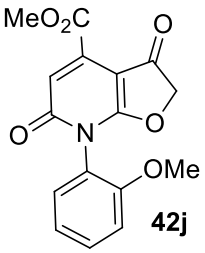
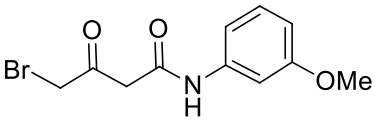
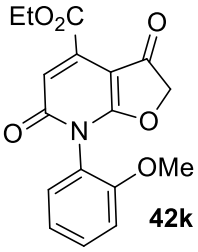
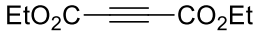
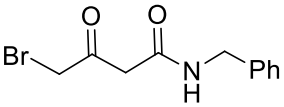
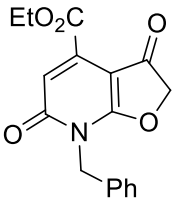
The reactions of 4-bromo-3-oxo-*N*-phenylbutanamide **39g** with activated alkynes **2** and **2f** afforded the corresponding 3(2*H*)-furanone fused 2-pyridones **42a** and **42b** in 47% and 37% yields respectively. Different analogues **42c** to **42f** were made in satisfactory yields by

introducing electron-donating substituents to the para-position of the aryl ring in 4-bromo-3-oxo-*N*-aryl-butanamide (such as in **39h** and **39i**). We could also provide additional support to the structure with the X-ray structure of **42c**. Chlorinated analogues of 3(2*H*)-furanone fused 2-pyridones **42g** to **42i** were made by starting from appropriately functionalized 4-bromo-3-oxo-*N*-aryl-butanamides **39j** and **39k**. Methoxy-substituent at the *ortho*-position of 3(2*H*)-furanone fused *N*-aryl-2-pyridone was introduced as in **42j** and **42k** from the reaction of **39l** with **2** and **2f** respectively. Finally, the reaction of diethylacetylene dicarboxylate **2f** with *N*-benzyl-4-bromo-3-oxobutanamide **39m** provided 3(2*H*)-furanone fused *N*-benzyl-2-pyridone **42l** in 40% yield.

Table 2.4. Generality of 3(2*H*)-furanone fused 2-pyridone synthesis with various activated alkynes and substituted 4-bromo-3-oxo-*N*-phenylbutanamide

Entry	Acetylene	4-Bromoacetoacetanillide	Product	Yield (%)
1	 **2**	 **39g**	 **42a**	47
2	 **2f**	 **39g**	 **42b**	37
3	 **2**	 **39h**	 **42c**	51

4	 **2f**	 **39h**	 **42d**	37
5	 **2**	 **39i**	 **42e**	38
6	 **2f**	 **39i**	 **42f**	35
7	 **2**	 **39j**	 **42g**	33
8	 **2**	 **39k**	 **42h**	45
9	 **2f**	 **39k**	 **42i**	42

10		**2**		**39l**	 **42j**	45
11		**2f**		**39l**	 **42k**	40
12		**2f**		**39m**	 **42l**	40

Reaction conditions: i. **2**(1.0 equiv.), **39** (1.1 equiv.), base (2.0 equiv.), THF, rt, 12 h
ii. Pivalic acid (10 equiv.), ^{i}PrOH, 100 ^{o}C, 12 h.

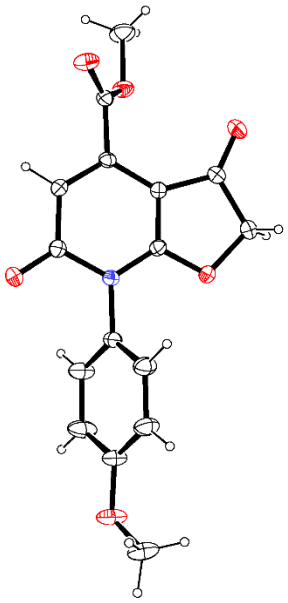
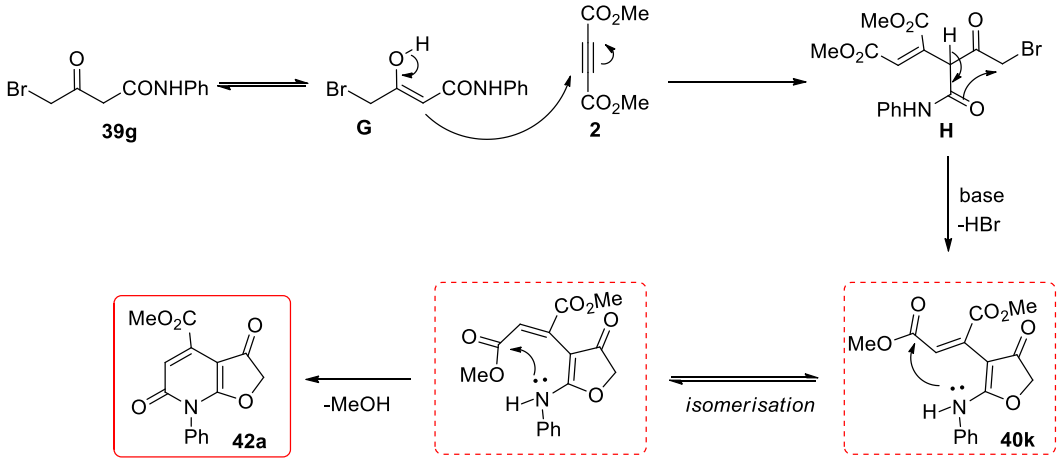


Fig 2.12. Single crystal X-ray of **42c** (CCDC: 2178732).

The initial steps towards the formation of 3(2*H*)-furanone fused 2-pyridone are the same as shown in Scheme 2.15. The Michael adduct **H** is formed by the addition of the enolate **G** to

activated alkyne. Intramolecular nucleophilic substitution occurs in **H** by the attack of ester enolate to the carbon bearing the halogen and this results in the formation of the 3(2*H*)-furanone intermediate **40k**. Acid induced isomerization of the double bond makes the terminal ester-carbonyl closer for the attack of the lone pair on *N*-atom which results in the formation of the 3(2*H*)-furanone fused 2-pyridone moiety with simultaneous elimination of MeOH (Scheme 2.32).



Scheme 2.32

2.5 Conclusions

In conclusion, we have developed a method for the synthesis of 4-vinyl-3(2*H*)-furanones from activated alkynes and 4-halo-1,3-dicarbonyl compounds. The expected 4-vinyl-3(2*H*)-furanone forms *via* tandem Michael addition followed by an intramolecular cyclization. We encountered the formation of a side-product (regioisomeric 4-vinyl-3(2*H*)-furanone) by a stepwise [2+2] cycloaddition between enolate (of the 4-halo-1,3-dicarbonyl compound) and activated alkyne followed by a sequential 4π-ring opening and an intramolecular cyclization. We also describe the formation of 3(2*H*)-furanone fused 2-pyridone from the reaction of 4-bromo-3-oxo-*N*-alkyl (aryl)butanamide with activated alkynes. All the reactions were found to be general affording the corresponding substituted/fused 3(2*H*)-furanones in satisfactory to good yields; currently the biological evaluation of the synthesized compounds is underway.

2.6 Experimental Section

2.6.1 General Experimental Methods. All chemicals were of the best grade commercially available and were used without further purification. All solvents were purified according to the standard procedures; dry solvents were obtained according to the literature methods and stored over molecular sieves. Analytical thin-layer chromatography was performed on

polyester sheets precoated with silica gel containing fluorescent indicator (POLYGRAMSIL G/UV254). Gravity column chromatography was performed using silica, and mixtures of ethyl acetate hexanes were used for elution. Melting points were measured with a Fisher John melting point apparatus and are uncorrected. NMR spectra were recorded with Bruker Avance-500 (500 MHz for ^{1}H NMR, 125 MHz for ^{13}C NMR) spectrophotometer instruments. All spectra were measured at 300 K, unless otherwise specified. The chemical shifts δ are given in ppm and referenced to the external standard TMS or internal solvent standard. ^{1}H NMR coupling constants (*J*) are reported in Hertz (Hz) and multiplicities are indicated as follows s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublets). Mass spectra were performed with a ThermoFinnigan MAT95XL, a ThermoFisher Scientific LTQ OrbitrapVelos, and an Agilent 6890 gas chromatograph with JMS-T100GC spectrometer or with a ESI/ HRMS at 60,000 resolution using Thermo Scientific Exactive mass spectrometer with orbitrapanalyzer.

All chemicals were purchased from TCI Chemicals, Sigma-Aldrich or Spectrochem. 4-Bromoacetoacetates and 4-bromo-3-oxo-*N*-phenylbutanamide and their derivatives were prepared by following reported procedures.[34-40]

2.6.2 Experimental procedure for the reaction between activated acetylene and 4-haloacetoacetate

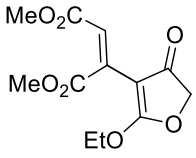
A mixture of activated acetylene (1.0 equiv.), 4-haloacetoacetate (1.1 equiv.) and sodium carbonate (2.0 equiv.) was weighed into a dry Schlenk tube. The tube was degassed and anhydrous THF (0.18 mM) was added after which the reaction mixture was stirred at RT. Upon completion of the reaction as indicated by TLC (12 h), the solvent was removed and the residue was subjected to column chromatography over silica gel (100-200 mesh), using mixtures of hexanes/ethyl acetate as eluents, affording the corresponding 4-vinyl-3(2*H*)-furanones.

Synthesis and characterization of 4-vinyl-3(2*H*)-furanones

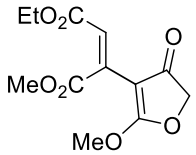
Dimethyl 2-(2-ethoxy-4-oxo-4,5-dihydrofuran-3-yl)maleate & **4-Ethyl 1-methyl 2-(2-methoxy-4-oxo-4,5-dihydrofuran-3-yl)maleate (40a** & **41a) :** The reaction was performed according to the general procedure with dimethyl acetylenedicarboxylate **2** (100 mg, 0.70 mmol), ethyl-4-chloroacetoacetate **39** (128 mg, 0.77 mmol) and Na_2CO_3 (150 mg, 1.42 mmol) at room temperature for 12 h. Upon completion of the reaction as indicated by TLC, the solvent was removed and the crude product was purified by silica gel (100-200 mesh) column chromatography (60% ethyl acetate in hexanes) to afford the products **40a** & **41a** (157 mg,

82%) as regioisomers in a ratio of 1:0.69. The regioisomers were further purified over 230-400 silica gel column chromatography using 40% ethyl acetate in hexane as eluent, which afforded the two regioisomers **40a** & **41a** as colorless solids respectively.

Analytical data of 40a & 41a as a mixture



&



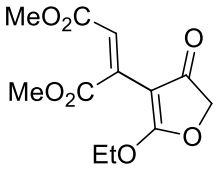
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 6.88 (s, 1H), 6.83 (s, 0.69H), 4.68 (s, 1.5H), 4.66 (s, 2H), 4.55 (q, *J* = 6.5 Hz, 2H), 4.20-4.17 (m, 4H), 3.89 (s, 6H), 3.72 (s, 3H), 1.47 (t, *J* = 7.0 Hz, 3H), 1.28 (t, *J* = 7.0 Hz, 2.6H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 192.0, 191.9, 180.6, 180.3, 167.4, 167.4, 166.6, 166.0, 137.6, 137.0, 113.4, 112.5, 90.5, 90.3, 75.3, 75.2, 68.0, 60.5, 57.8, 52.5, 52.3, 51.6, 14.5, 14.2 ppm.

HRMS(ESI-Orbitrap) m/z: $(M+Na)^+$ calcd for $C_{12}H_{14}O_7Na$: 293.0632; Found: 293.0655.

Analytical data of 40a

Mp: 152-154^{o}C



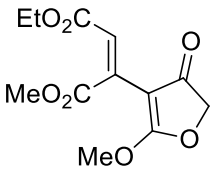
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 6.88 (s, 1H), 4.66 (s, 2H), 4.55 (q, *J* = 7.0 Hz, 2H), 3.88 (s, 3H), 3.72 (s, 3H), 1.47 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 192.0, 180.3, 167.4, 166.6, 137.6, 112.5, 90.0, 75.2, 68.0, 52.4, 51.6, 14.5 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$ calcd for $C_{12}H_{14}O_7Na$: 293.0632; Found: 293.0632.

Analytical data of 41a

Mp: 124-126 ^{o}C



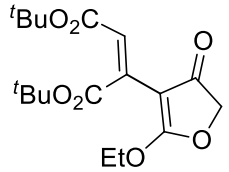
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 6.82 (s, 1H), 4.67 (s, 2H), 4.19-4.15 (m, 5H), 3.88 (s, 3H), 1.27 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 192.0, 180.7, 167.5, 166.1, 137.0, 113.3, 90.5, 75.3, 60.5, 57.8, 52.5, 14.2 ppm.

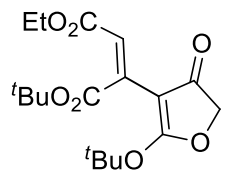
HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$ calcd for $C_{12}H_{14}O_7Na$: 293.0632; Found: 293.0643.

Di-*tert*-butyl 2-(2-ethoxy-4-oxo-4, 5-dihydrofuran-3-yl)maleate & **1-(*tert*-butyl) 4-ethyl 2-(2-(*tert*-butoxy)-4-oxo-4,5-dihydrofuran-3-yl)maleate (40b** & **41b):** The reaction was performed according to the general procedure with di-*tert*-butyl acetylenedicarboxylate **2b** (100 mg, 0.44 mmol), ethyl-4-chloroacetoacetate **39** (80 mg, 0.49 mmol) and Na_2CO_3 (94 mg, 0.88 mmol) at room temperature for 12 h. Upon completion of the reaction as indicated by TLC, the solvent was removed and the crude product was purified by silica gel (100-200 mesh) column chromatography (30% ethyl acetate in hexanes) to afford the desired products **40b** & **41b** as a regioisomeric mixture (61 mg, 39 %) in a ratio of 1:0.62.

Analytical data of 40b & 41b as a mixture



&



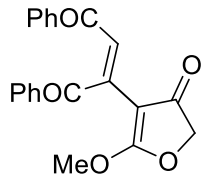
^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 6.68 (s, 1H), 6.58 (s, 0.62H), 4.60 (s, 1.2H), 4.56 (s, 2H), 4.49 (q, *J* = 7.0 Hz, 2H), 4.40 (q, *J* = 7.0 Hz, 1.2H), 1.49 (s, 9H), 1.42 (s, 5.3H), 1.40-1.37 (m, 18H), 1.34 (t, *J* = 7.0 Hz, 2H)

^{13}C{1H} NMR ($CDCl_3$, 125 MHz) δ (ppm): 192.6, 191.7, 180.3, 180.1, 165.5, 165.2, 164.6, 164.5, 136.4, 132.0, 129.8, 116.1, 91.1, 90.7, 82.1, 81.2, 81.0, 80.0, 75.4, 75.0, 67.7, 66.6, 28.1, 28.0, 27.9, 27.8, 14.8, 14.6

HRMS (ESI-Orbitrap) m/z: (M+Na)+calcd for $C_{18}H_{26}O_7Na$: 377.1571; Found: 377.1574.

(*Z*)-2-(2-methoxy-4-oxo-4,5-dihydrofuran-3-yl)-1,4-diphenylbut-2-ene-1,4-dione (40c): The reaction was performed according to the general procedure with1,4-diphenylbut-2-yne-1,4-dione **2c** (100 mg, 0.43 mmol), methyl-4-chloroacetoacetate **39f** (71 mg, 0.47 mmol) and Na_2CO_3 (91 mg, 0.86 mmol), at room temperature for 12 h. Upon completion of the reaction as indicated by TLC, the solvent was removed and the crude product was purified by silica gel (100-200 mesh) column chromatography (20% ethyl acetate in hexanes) to afford the desired product **40c** as pale-yellow viscous liquid (45 mg, 30%).

Analytical data of 40c



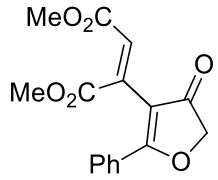
^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): δ 7.94 (2H, d, *J* = 7.5 Hz), 7.69 (2H, d, *J* = 8.0 Hz), 7.64 (1H, t, *J* = 7.0 Hz), 7.53-7.48 (3H, m), 7.41 (2H, t, *J* = 7.5 Hz), 6.05 (1H, s), 4.88 (2H, s), 3.52 (3H, s)

^{13}C{1H} NMR ($CDCl_3$, 125 MHz) δ (ppm): 192.5, 185.8, 169.0, 165.3, 153.4, 134.4, 134.2, 132.7, 132.3, 130.2, 129.5, 128.9, 127.6, 101.0, 77.7, 52.4

HRMS (ESI-Orbitrap) m/z: (M+Na)+calcd for $C_{21}H_{16}NaO_5$: 371.0890; Found: 371.0910.

Dimethyl 2-(4-oxo-2-phenyl-4,5-dihydrofuran-3-yl)maleate (40d): The reaction was performed according to the general procedure with dimethyl acetylenedicarboxylate **2** (100 mg, 0.70 mmol), 4-bromo-1-phenylbutane-1,3-dione **39b** (188 mg, 0.77 mmol) and Na_2CO_3 (150 mg, 1.42 mmol), at room temperature for 12 h. Upon completion of the reaction as indicated by TLC, the solvent was removed and the crude product was purified by silica gel (100-200 mesh) column chromatography (30% ethyl acetate in hexanes) to afford the desired product **40d** (109 mg, 51%) as pale-yellow viscous liquid.

Analytical data of 40d



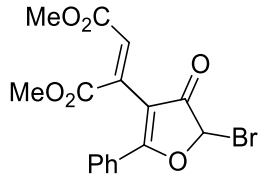
^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 7.61-7.58 (m, 2H), 7.46 (t, *J* = 7.0 Hz, 1H), 7.42-7.37 (m, 2H), 7.03 (s, 1H), 4.74 (s, 2H), 3.65 (s, 3H), 3.48 (s, 3H)

^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ (ppm): δ 198.4,198.0, 182.5, 165.5, 165.1, 133.3, 132.7, 132.4, 131.6, 129.9, 128.8, 128.6, 128.5, 127.7, 124.2, 111.1, 74.6, 52.8, 52.1

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$calcd for $C_{16}H_{14}O_6Na$: 325.0683; Found: 325.0695.

Dimethyl 2-(5-bromo-4-oxo-2-phenyl-4,5-dihydrofuran-3-yl)maleate (40e): The reaction was performed according to the general procedure with dimethyl acetylenedicarboxylate **2** (100 mg, 0.70 mmol), 4,4-dibromo-1-phenylbutane-1,3-dione **39c** (248 mg, 0.77 mmol) and Na_2CO_3 (150 mg, 1.42 mmol) at room temperature for 12 h. Upon completion of the reaction as indicated by TLC, the solvent was removed and the crude product was purified by silica gel

(100-200 mesh) column chromatography (30% ethyl acetate in hexanes) to afford the desired product **40e** as pale-yellow viscous liquid (29 mg, 11%).



Analytical data of 40d

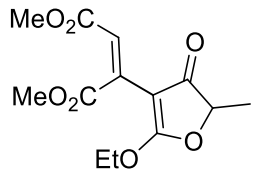
^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): δ 7.70 (d, *J* = 7.5 Hz, 2H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.49-7.46 (m, 2H), 7.19 (s, 1H), 6.57 (s, 1H), 3.74 (s, 3H), 3.60 (s, 3H)

^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ (ppm): δ 194.1, 179.2, 164.9, 164.7, 133.2, 132.9, 129.0, 128.7, 128.0, 108.8, 73.1, 53.0, 52.3

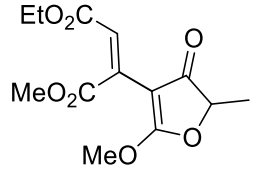
HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$calcd for $C_{16}H_{13}BrO_6Na$:402.9788; Found: 402.9804.

Dimethyl 2-(2-ethoxy-5-methyl-4-oxo-4,5-dihydrofuran-3-yl)maleate & **4-ethyl 1-methyl 2-(2-methoxy-5-methyl-4-oxo-4,5-dihydrofuran-3-yl)maleate (40f** & **41f):** The reaction was performed according to the general procedure with dimethyl acetylenedicarboxylate **2** (100 mg, 0.70 mmol), ethyl-4-bromo-3-oxopentanoate **59d** (174 mg, 0.77 mmol) and Na_2CO_3 (150 mg, 1.42 mmol) at room temperature for 12 h. Upon completion of the reaction as indicated by TLC, the solvent was removed and the crude product was purified by silica gel (100-200 mesh) column chromatography (30% ethyl acetate in hexanes) to afforded the desired products **40f** & **41f** (161 mg, 80%) as regioisomers in a ratio of 1:0.30.

Analytical data of 40f & **41f as a mixture**



&

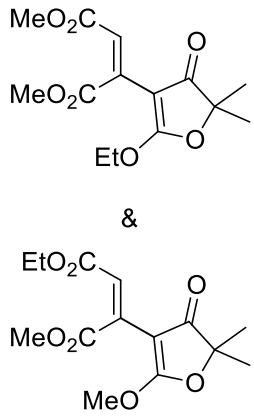


^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 6.87 (s, 1H), 6.78 (s, 0.30H), 4.81-4.73 (m, 1.4H), 4.54 (q, *J* = 7.0 Hz, 2H), 4.47 (q, *J* = 7.0 Hz, 0.60 H), 3.89 (s, 3H), 3.80 (s, 1H), 3.74 (s, 1H), 3.72 (s, 3H), 1.57-1.53 (m, 5H), 1.47 (t, *J*= 7.0 Hz, 3H) 1.40 (t, *J* =7.0 Hz, 1H) ppm.

^{13}C{^{1}H}NMR (125 MHz, $CDCl_3$): δ 194.8, 194.4, 179.0, 178.8, 167.5, 166.7, 166.1, 165.4, 138.1, 131.9, 129.0, 128.1, 112.0, 89.0, 84.2, 84.1, 67.8, 66.6, 60.8, 56.6, 52.7, 52.3, 51.8, 51.6, 16.4, 16.2, 14.6, 14.4 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$calcd for $C_{13}H_{16}O_7Na$: 307.0788; Found: 307.0790.

Dimethyl 2-(2-ethoxy-5,5-dimethyl-4-oxo-4,5-dihydrofuran-3-yl)maleate& **4-Ethyl 1-methyl 2-(2-methoxy-5,5-dimethyl-4-oxo-4,5-dihydrofuran-3-yl)maleate (40g** & **41g) :** The reaction was performed according to the general procedure with dimethyl acetylenedicarboxylate **2** (100 mg, 0.70 mmol), ethyl-4-bromo-4-methyl-3-oxopentanoate **39e** (184 mg, 0.77 mmol) and Na_2CO_3 (150 mg, 1.42 mmol) at room temperature for 12 h. Upon completion of the reaction as indicated by TLC, the solvent was removed and the crude product was purified by silica gel (100-200 mesh) column chromatography (20% ethyl acetate in hexanes) to afford the desired products **40g** & **41 g** (119 mg, 57%) as regioisomers in a ratio of 1:0.65.



Analytical data of 40g & **41g as a mixture**

^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): δ 6.82 (s, 1H), 6.60 (s, 0.65H), 4.22-4.12 (m, 3.4H), 3.77-3.76 (m, 4H), 3.70 (s, 3.4H), 1.94 (s, 3.3H), 1.83 (s, 4H), 1.25 (t, *J* = 7.0 Hz, 3H), 1.22-1.17 (m, 2H)

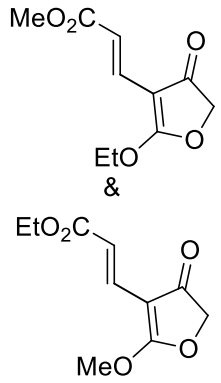
^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ (ppm): 198.6, 198.1, 170.4, 169.9, 168.3, 166.5, 166.1, 165.0, 140.3, 140.0, 139.5, 129.6, 129.3, 128.9, 69.4, 65.1, 61.5, 61.1, 61.1, 53.0, 52.9, 52.2, 52.0, 51.0, 33.1, 32.9, 30.7, 30.1, 30.0, 14.1, 14.1

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$calcd for $C_{14}H_{18}O_7Na$: 321.0945; Found: 321.0952.

Methyl (*E*)-3-(2-ethoxy-4-oxo-4,5-dihydrofuran-3-yl)acrylate & **Ethyl (*E*)-3-(2-methoxy-4-oxo-4,5-dihydrofuran-3-yl)acrylate (40h & 41h):** The reaction was performed according to the general procedure with methyl propiolate **2d** (100 mg, 1.19 mmol), ethyl-4-chloroacetoacetate **39** (215 mg, 1.31 mmol) and Na_2CO_3 (252 mg, 2.38 mmol) at room temperature for 12 h. Upon completion of the reaction as indicated by TLC, the solvent was removed and the crude product was purified by silica gel (100-200 mesh) column chromatography (50% ethyl acetate in hexanes) to afford the desired product **40h** & **41h** (105 mg, 42%) as regioisomers in a ratio of 1:0.20.

Analytical data of 40h & **41h as a mixture**

^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): δ 7.23-7.17 (m, 1.30H), 6.59-6.54 (m, 1.17H), 4.61 (s, 0.41H), 4.59 (s, 2H), 4.51 (q, *J* = 7.0 Hz, 2H), 4.15-



4.11 (m, 1H), 3.67 (s, 3H), 1.43 (t, *J* = 7.0 Hz, 3H), 1.22 (t, *J* = 7.0 Hz, 1H)

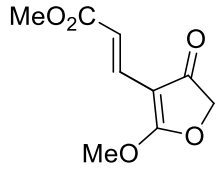
$^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz) δ (ppm): 192.8, 181.8, 181.6, 168.4, 167.8, 130.6, 130.0, 115.6, 114.8, 92.5, 75.6, 75.5, 67.5, 60.0, 57.2, 51.3, 14.6, 14.3

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$calcd for $C_{10}H_{12}O_5Na$: 235.0577; Found: 235.0579

Methyl (*E*)-3-(2-methoxy-4-oxo-4,5-dihydrofuran-3-yl)acrylate (40i): The reaction was performed according to the general procedure with methyl propiolate **2d** (100 mg, 1.19 mmol), methyl-4-chloroacetoacetate **39f** (197 mg, 1.31 mmol) and Na_2CO_3 (252 mg, 2.38 mmol) at room temperature for 12 h. Upon completion of the reaction as indicated by TLC, the solvent was removed and the crude product was purified by silica gel (100-200 mesh) column chromatography (50% ethyl acetate in hexanes) to afford the desired product **3i** as colourless solid (129 mg, 55%).

Analytical data of 40i

Mp: 62-64 ^{o}C



^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): δ 7.20 (d, *J* = 16 Hz, 1H), 6.56 (d, *J* = 15.5 Hz, 1H), 4.62 (s, 2H), 4.12 (s, 3H), 3.67 (s, 3H)

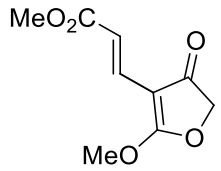
$^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz) δ (ppm): 192.8, 181.9, 168.3, 130.3, 115.2, 92.6, 75.6, 57.2, 51.3

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$calcd for $C_9H_{10}O_5Na$: 221.0420; Found: 221.0425.

Ethyl (*E*)-3-(2-ethoxy-4-oxo-4,5-dihydrofuran-3-yl)acrylate (40j): The reaction was performed according to the general procedure with ethyl propiolate **1e** (100 mg, 1.02 mmol), ethyl-4-chloroacetoacetate **39** (184 mg, 1.12 mmol) and Na_2CO_3 (238 mg, 2.24 mmol) at room temperature for 12 h. Upon completion of the reaction as indicated by TLC, the solvent was removed and the crude product was purified by silica gel (100-200 mesh) column chromatography (50% ethyl acetate in hexanes) to afford the desired product **40j** as pale-yellow solid (110 mg, 48%).

Analytical data of 40j

Mp: 68-70 ^{o}C



^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): δ 7.21 (d, *J* = 16 Hz, 1H), 6.57 (d, *J* = 16 Hz, 1H), 4.59 (s, 2H), 4.51 (q, *J* = 7.0 Hz, 2H), 4.13 (q, *J* = 7.0 Hz, 2H), 1.43 (t, *J* = 7.0 Hz, 3H), 1.22 (t, *J* = 7.0 Hz, 3H)

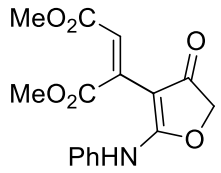
^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ (ppm): 192.8, 181.6, 168.0, 130.2, 115.5, 115.3, 92.5, 75.5, 67.4, 60.0, 14.7, 14.3

HRMS (ESI-Orbitrap) m/z: $(M+Na)^{+}$calcd for $C_{11}H_{14}O_5Na$: 249.0733; Found: 249.0717.

Dimethyl 2-(4-oxo-2-(phenylamino)-4,5-dihydrofuran-3-yl)maleate (40k): The reaction was performed according to the general procedure with dimethyl acetylenedicarboxylate **2** (100 mg, 0.70 mmol), 4-bromo-3-oxo-*N*-phenylbutanamides **39g** (198 mg, 0.77 mmol) and Na_2CO_3 (150 mg, 1.42 mmol) at room temperature for 12 h. Upon completion of the reaction as indicated by TLC, the solvent was removed and the crude product was purified by silica gel (100-200 mesh) column chromatography (20% ethyl acetate in hexanes) to afford the desired product **40k** as pale-yellow solid (87 mg, 39%).

Analytical data of 40k

Mp: 108-110 ^{o}C



^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): δ 8.83 (brs, 1H), 7.29 (t, *J* = 7.5 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.13 (t, *J* = 7.5 Hz, 1H), 6.79 (s, 1H), 4.56 (s, 2H), 3.83 (s, 3H), 3.64 (s, 3H)

^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ (ppm): 190.8, 173.6, 171.1, 166.8, 136.6, 135.5, 129.4, 125.9, 121.6, 115.9, 89.0, 74.2, 53.5, 51.7

HRMS (ESI-Orbitrap) m/z: $(M+Na)^{+}$calcd for $C_{16}H_{15}NO_6Na$: 340.0792; Found: 340.0793.

2.6.3 Experimental procedure for the synthesis of 3(2*H*)-furanone fused 2-pyridone from activated acetylene and 4-bromo-3-oxo-*N*-phenylbutanamides: A mixture of activated acetylene (1.0 equiv.), 4-bromo-3-oxo-*N*-phenylbutanamide (1.1 equiv.) and sodium carbonate (2.0 equiv.) was weighed into a dry Schlenk tube. The tube was degassed and anhydrous THF

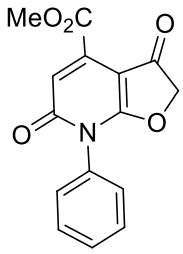
(0.18 mM) was added and the reaction mixture was stirred at RT. Upon completion of the reaction (12 h), the solvent was removed and to the residue, isopropanol was added followed by pivalic acid (10 equiv.) and the reaction mixture was allowed to stir at 100 °C for 12 h. Upon completion of the reaction, the solvent was removed and the residue was subjected to column chromatography over silica gel (100-200 mesh), using mixtures of hexanes/ethyl acetate as eluent to afford the corresponding 3(2*H*)-furanone fused 2-pyridone.

Synthesis and characterization of 3(2*H*)-furanone fused 2-pyridones

Methyl 3,6-dioxo-7-phenyl-2,3,6,7-tetrahydrofuro[2,3-*b*]pyridine-4-carboxylate (42a): The reaction was performed according to the general procedure with dimethyl acetylenedicarboxylate **2** (50 mg, 0.35 mmol), 4-bromo-3-oxo-*N*-phenylbutanamide **39g** (99 mg, 0.39 mmol) and Na_2CO_3 (75 mg, 0.70 mmol) at room temperature for 12 h. Upon completion of the reaction (12 h), the solvent was removed and to the residue isopropanol (2 mL) was added followed by pivalic acid (397 µL, 3.52 mmol) and the reaction mixture was stirred at 100 °C for 12h. The crude product was purified over silica gel (100-200 mesh) column chromatography (40% ethyl acetate in hexanes) to afford the desired product **42a** as pale-yellow solid (47 mg, 47%).

Analytical data of 42a

Mp: 138-142 °C



^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): δ 7.51-7.47 (m, 3H), 7.25-7.23 (m, 2H), 6.59 (s, 1H), 4.65 (s, 2H), 3.91 (s, 3H)

^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ (ppm): 187.4, 174.5, 163.9, 161.8, 138.5, 131.8, 130.2, 129.8, 127.6, 115.4, 95.4, 77.0, 53.2

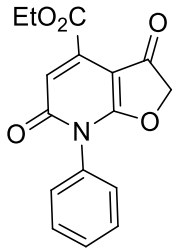
HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$calcd for $C_{15}H_{11}NO_5Na$: 308.0529; Found: 308.0533.

Ethyl 3,6-dioxo-7-phenyl-2,3,6,7-tetrahydrofuro[2,3-*b*]pyridine-4-carboxylate (42b): The reaction was performed according to the general procedure with diethyl acetylenedicarboxylate **2f** (50 mg, 0.28 mmol), 4-bromo-3-oxo-*N*-phenylbutanamide **39g** (80 mg, 0.31 mmol) and Na_2CO_3 (59 mg, 0.56 mmol) at room temperature for 12 h. Upon completion of the reaction (12 h), the solvent was removed and to the residue isopropanol (2 mL) was added followed by pivalic acid (290 µL, 2.84 mmol) and the reaction mixture was stirred at 100 °C for 12h. The

crude product was purified over silica gel (100-200 mesh) column chromatography (40% ethyl acetate in hexanes) to afford the desired product **42b** as colourless solid (32 mg, 37%).

Analytical data of 42b

Mp: 128-132 ^{o}C



^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): δ 7.61-7.55 (m, 3H), 7.33 (d, *J* = 7.0 Hz, 2H), 6.69 (s, 1H), 4.75 (s, 2H), 4.47 (q, *J* = 7.0 Hz, 2H), 1.44 (t, *J* = 7.0 Hz, 3H)

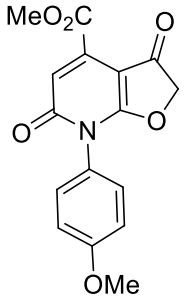
^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ (ppm): 187.3, 174.5, 163.5, 161.8, 139.0, 131.8, 130.2, 129.8, 127.6, 115.2, 95.5, 77.0, 62.6, 14.0

HRMS (ESI-Orbitrap) m/z: $(M+Na)^{+}$calcd for $C_{16}H_{13}NO_5Na$: 322.0686; Found: 322.0702.

Methyl 7-(4-methoxyphenyl)-3,6-dioxo-2,3,6,7-tetrahydrofuro[2,3-*b*]pyridine-4-carboxylate (42c): Following 4-bromo-*N*-(4-methoxyphenyl)-3-oxobutanamide **39h** (110 mg, 0.39 mmol) and Na_2CO_3 (75 mg, 0.70 mmol) at room temperature for 12 h. Upon completion of the reaction (12 h), the solvent was removed and to the residue isopropanol (2 mL) was added followed by pivalic acid (397 µL, 3.52 mmol) and the reaction mixture was stirred at 100 ^{o}C for 12h. The crude product was purified over silica the general experimental procedure with dimethyl acetylenedicarboxylate **2** (50 mg, 0.35 mmol), gel (100-200 mesh) column chromatography (50% ethyl acetate in hexanes) to afford the desired product **42c** as pale-yellow solid (56 mg, 51%).

Analytical data of 42c

Mp: 154-158 ^{o}C



^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): δ 7.24 (d, *J* = 8.5 Hz, 2H), 7.08 (d, *J* = 8.5 Hz, 2H), 6.69 (s, 1H), 4.75 (s, 2H), 4.01 (s, 3H), 3.89 (s, 3H)

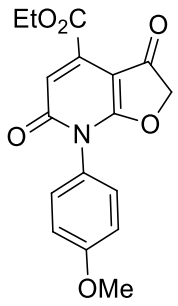
^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ (ppm): 187.4, 174.8, 164.0, 162.1, 160.6, 138.4, 128.7, 124.0, 115.4, 115.1, 95.4, 77.0, 55.6, 53.2

HRMS (ESI-Orbitrap) m/z: $(M+Na)^{+}$calcd for $C_{16}H_{13}NO_6Na$: 338.0635; Found: 338.0642.

Ethyl 7-(4-methoxyphenyl)-3,6-dioxo-2,3,6,7-tetrahydrofuro[2,3-*b*]pyridine-4-carboxylate (42d): Following the general experimental procedure with diethyl acetylenedicarboxylate **2f** (50 mg, 0.28 mmol), 4-bromo-*N*-(4-methoxyphenyl)-3-oxobutanamide **39h** (89 mg, 0.31 mmol) and Na_2CO_3 (59 mg, 0.56 mmol) at room temperature for 12 h. Upon completion of the reaction (12 h), the solvent was removed and to the residue isopropanol (2 mL) was added followed by pivalic acid (290 µL, 2.84 mmol) and the reaction mixture was stirred at 100 °C for 12h.The crude product was purified over silica gel (100-200 mesh) column chromatography (40% ethyl acetate in hexanes) to afford the desired product **42d** as pale-yellow solid (32 mg, 37%).

Analytical data of 42d

Mp: 116-118 °C



^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): δ 7.24 (d, *J* = 8.0 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 2H), 6.68 (s, 1H), 4.74 (s, 2H), 4.47 (q, *J* = 7.0 Hz, 2H), 3.89 (s, 3H), 1.43 (t, *J* = 7.0 Hz, 3H)

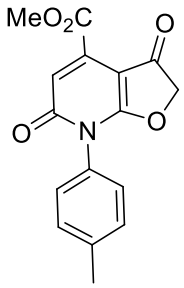
^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ (ppm): 187.4, 174.7, 163.5, 162.1, 160.6, 138.9, 128.7, 124.0, 115.0, 95.5, 77.0, 62.5, 55.6, 14.0

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$calcd for $C_{17}H_{16}NO_6$: 330.0972; Found: 330.0968.

Methyl 3,6-dioxo-7-(*p*-tolyl)-2,3,6,7-tetrahydrofuro[2,3-*b*]pyridine-4-carboxylate (42e): Following the general experimental procedure with dimethyl acetylenedicarboxylate **2** (50 mg, 0.35 mmol), 4-bromo-3-oxo-*N*-(*p*-tolyl)butanamide **39i** (105 mg, 0.39 mmol), Na_2CO_3 (75 mg, 0.70 mmol) at room temperature for 12 h. Upon completion of the reaction (12 h), the solvent was removed and to the residue isopropanol (2 mL) was added followed by pivalic acid (397 µL, 3.52 mmol) and the reaction mixture was stirred at 100 °C for 12h. The crude product was purified over silica gel (100-200 mesh) column chromatography (50% ethyl acetate in hexanes) to afford the desired product **42e** as pale-yellow solid (40 mg, 38%).

Analytical data of 42e

Mp: 160-164 °C



^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): δ 7.39 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 6.68 (s, 1H), 4.74 (s, 2H), 4.00 (s, 3H), 2.46 (s, 3H)

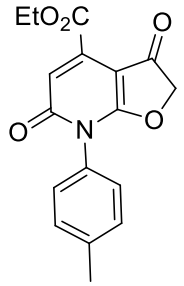
$^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz) δ (ppm): 187.3, 174.6, 164.0, 161.9, 140.5, 138.4, 130.5, 129.0, 127.3, 115.5, 95.4, 53.2, 21.3

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$calcd for $C_{16}H_{13}NO_5Na$: 322.0686; Found: 322.0693.

Ethyl 3,6-dioxo-7-(*p*-tolyl)-2,3,6,7-tetrahydrofuro[2,3-*b*]pyridine-4-carboxylate (42f): Following the general experimental procedure with diethyl acetylenedicarboxylate **2f** (50 mg, 0.28 mmol), 4-bromo-3-oxo-*N*-(*p*-tolyl)butanamide **39i** (84 mg, 0.31 mmol) and Na_2CO_3 (59 mg, 0.56 mmol) at room temperature for 12 h. Upon completion of the reaction (12 h), the solvent was removed and to the residue isopropanol (2 mL) was added followed by pivalic acid (290 µL, 2.84 mmol) and the reaction mixture was stirred at 100 °C for 12h. The crude product was purified over silica gel (100-200 mesh) column chromatography (40% ethyl acetate in hexanes) to afford the desired product **42f** as colourless solid (31 mg, 35%).

Analytical data of 42f

Mp: 160-164 °C



^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): δ 7.30 (d, *J* = 8.0 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 6.59 (s, 1H), 4.65 (s, 2H), 4.38 (q, *J* = 7.0 Hz, 2H), 2.37 (s, 3H), 1.34 (t, *J* = 7.0 Hz, 3H)

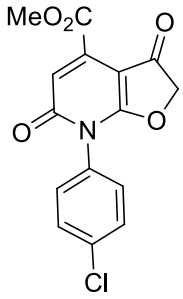
$^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz) δ (ppm): 187.3, 174.6, 163.5, 162.0, 140.5, 138.9, 130.5, 129.1, 127.3, 115.2, 95.5, 77.0, 62.5, 21.3, 14.0

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$calcd for $C_{17}H_{15}NO_5Na$: 336.0842; Found: 336.0849.

Methyl 7-(4-chlorophenyl)-3,6-dioxo-2,3,6,7-tetrahydrofuro[2,3-*b*]pyridine-4-carboxylate (42g): Following the general experimental procedure with dimethyl acetylenedicarboxylate **2** (50 mg, 0.35 mmol), 4-bromo-*N*-(4-chlorophenyl)-3-oxobutanamide **39j** (112 mg, 0.39 mmol) and Na_2CO_3 (75 mg, 0.70 mmol) at room temperature for 12 h. Upon completion of the reaction (12 h), the solvent was removed and to the residue isopropanol (2 mL) was added followed by pivalic acid (397 µL, 3.52 mmol) and the reaction mixture was stirred at 100 °C for 12h. The crude product was purified over silica gel (100-200 mesh) column

chromatography (50% ethyl acetate in hexanes) to afford the desired product **42g** as colourless solid (37 mg, 33%).

Analytical data of 42g



Mp: 168-172 ^{o}C

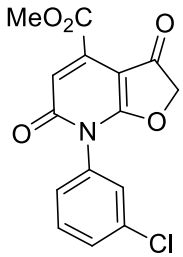
^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): δ 7.56 (d, *J* = 8.5 Hz, 2H), 7.29-7.27 (m, 2H), 6.69 (s, 1H), 4.76 (s, 2H), 4.00 (s, 3H)

^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ (ppm): 187.2, 174.3, 163.8, 161.5, 138.7, 136.4, 130.1, 130.0, 129.1, 115.4, 95.5, 77.0, 53.2

HRMS (ESI-Orbitrap) m/z: $(M+H)^{+}$calcd for $C_{15}H_{11}ClNO_5$: 320.0320; Found: 320.0320.

Methyl 7-(3-chlorophenyl)-3,6-dioxo-2,3,6,7-tetrahydrofuro[2,3-*b*]pyridine-4-carboxylate (42h): Following the general experimental procedure with dimethyl acetylenedicarboxylate **2** (50 mg, 0.35 mmol), 4-bromo-*N*-(3-chlorophenyl)-3-oxobutanamide **39k** (112 mg, 0.39 mmol) and Na_2CO_3 (75 mg, 0.70 mmol) at room temperature for 12 h. Upon completion of the reaction (12 h), the solvent was removed and to the residue isopropanol (2 mL) was added followed by pivalic acid (397 µL, 3.52 mmol) and the reaction mixture was stirred at 100 ^{o}C for 12h. The crude product was purified over silica gel (100-200 mesh) column chromatography (50% ethyl acetate in hexanes) to afford the desired product **42h** as pale-yellow solid (50 mg, 45%).

Analytical data of 42h



Mp: 148-152 ^{o}C

^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): δ 7.56-7.51 (m, 2H), 7.36 (s, 1H), 7.25 (d, *J* = 7.0 Hz, 2H) 6.69 (s, 1H), 4.77 (s, 2H), 4.01 (s, 3H)

^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ (ppm): 187.1, 174.2, 163.8, 161.4, 138.7, 135.4, 132.6, 130.7, 130.5, 128.1, 126.1, 115.4, 95.5, 77.1, 53.3

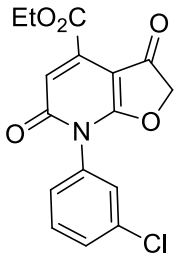
HRMS (ESI-Orbitrap) m/z: $(M+Na)^{+}$calcd for $C_{15}H_{10}ClNO_5Na$: 342.0140; Found: 340.0240.

Ethyl 7-(3-chlorophenyl)-3,6-dioxo-2,3,6,7-tetrahydrofuro[2,3-*b*]pyridine-4-carboxylate (42i) : Following the general experimental procedure with diethyl acetylenedicarboxylate **2f**

(50 mg, 0.28 mmol), 4-bromo-*N*-(3-chlorophenyl)-3-oxobutanamide **39k** (91 mg, 0.31 mmol) and Na_2CO_3 (59 mg, 0.56 mmol) at room temperature for 12 h. Upon completion of the reaction (12 h), the solvent was removed and to the residue isopropanol (2 mL) was added followed by pivalic acid (290 µL, 2.84 mmol) and the reaction mixture was stirred at 100 °C for 12h. The crude product was purified over silica gel (100-200 mesh) column chromatography (40% ethyl acetate in hexanes) to afford the desired product **42i** as pale-yellow solid (40 mg, 42%).

Analytical data of 42i

Mp: 116-118 °C



^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): δ 7.47-7.42 (m, 2H), 7.27 (s, 1H), 7.15 (d, *J* = 7.0 Hz, 2H), 6.59 (s, 1H), 4.68 (s, 2H), 4.38 (q, *J* = 7.0 Hz, 2H), 1.34 (t, *J* = 7.0 Hz, 3H)

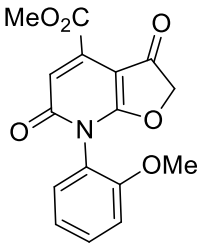
^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ (ppm): 187.1, 174.2, 163.3, 161.5, 139.2, 135.4, 132.7, 130.7, 130.5, 128.1, 126.1, 115.2, 95.6, 77.1, 62.6, 14.0

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$calcd for $C_{16}H_{13}ClNO_5$: 334.0477; Found: 334.0476

Methyl 7-(2-methoxyphenyl)-3,6-dioxo-2,3,6,7-tetrahydrofuro[2,3-*b*]pyridine-4-carboxylate (42j) : Following the general experimental procedure with dimethyl acetylenedicarboxylate **2** (50 mg, 0.35 mmol), 4-bromo-*N*-(2-methoxyphenyl)-3-oxobutanamide **39l** (111 mg, 0.39 mmol) and Na_2CO_3 (75 mg, 0.70 mmol) at room temperature for 12 h. Upon completion of the reaction (12 h), the solvent was removed and to the residue isopropanol (4 mL) was added followed by pivalic acid (397 µL, 3.52 mmol) and the reaction mixture was stirred at 100 °C for 1h. The crude product was purified over silica gel (100-200 mesh) column chromatography (50% ethyl acetate in hexanes) to afford the desired product **42j** as pale-yellow solid (50 mg, 45%).

Analytical data of 42j

Mp: 182-186 °C



^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): δ 7.44 (t, *J* = 7.0 Hz, 1H), 7.17 (d, *J* = 7.5 Hz, 1H), 7.05-7.01 (m, 2H) 6.58 (s, 1H), 4.63 (s, 2H), 3.91 (s, 3H), 3.74 (s, 3H)

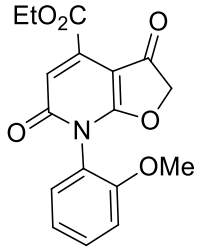
^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ (ppm): 187.5, 175.0, 164.1, 161.5, 154.4, 138.4, 131.8, 129.1, 121.1, 120.4, 115.4, 112.3, 95.3, 56.0, 53.2

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$calcd for $C_{16}H_{14}NO_6$: 316.0816; Found: 316.0812.

Ethyl 7-(2-methoxyphenyl)-3,6-dioxo-2,3,6,7-tetrahydrofuro[2,3-*b*]pyridine-4-carboxylate (42k) : Following the general experimental procedure, diethyl acetylenedicarboxylate **2f** (50 mg, 0.28 mmol), 4-bromo-*N*-(2-methoxyphenyl)-3-oxobutanamide **39l** (89 mg, 0.31 mmol) and Na_2CO_3 (59 mg, 0.56 mmol) at room temperature for 12 h. Upon completion of the reaction (12 h), the solvent was removed and to the residue isopropanol (3 mL) was added followed by pivalic acid (290 µL, 2.84 mmol) and the reaction mixture was stirred at 100 ^{o}C for 12h.The crude product was purified over silica gel (100-200 mesh) column chromatography (50% ethyl acetate in hexanes) to afford the desired product **42k** as pale-yellow solid (37 mg, 40%).

Analytical data of 42k

Mp: 130-132 ^{o}C



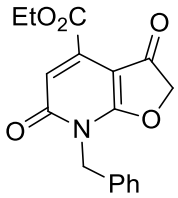
^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): δ 7.44 (t, *J* = 7.5 Hz, 1H), 7.17 (d, *J* = 8.0 Hz, 1H), 7.06-7.02 (m, 2H), 6.58 (s, 1H), 4.63 (s, 2H), 4.38 (q, *J* = 7.0 Hz, 2H), 3.75 (s, 3H), 1.35 (t, *J* = 7.0 Hz,3H)

^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ (ppm): 187.4, 175.0, 163.7, 161.6, 154.5, 138.9, 131.8, 129.1, 121.1, 120.5, 115.2, 112.4, 95.3, 77.0, 62.4, 55.9, 14.0

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$calcd for $C_{17}H_{15}NO_6Na$: 352.0792; Found: 352.0795.

Ethyl 7-benzyl-3,6-dioxo-2,3,6,7-tetrahydrofuro[2,3-*b*]pyridine-4-carboxylate) (42l) : Following the general experimental procedure, diethyl acetylenedicarboxylate **2f** (50 mg, 0.28 mmol), *N*-benzyl-4-bromo-3-oxobutanamide **39m** (84 mg, 0.31 mmol) and Na_2CO_3 (59 mg, 0.56 mmol) at room temperature for 12 h. Upon completion of the reaction (12 h), the solvent

was removed and to the residue isopropanol (4 mL) was added followed by pivalic acid (290 µL, 2.84 mmol) and the reaction mixture was stirred at 100 °C for 1h. The crude product was purified over silica gel (100-200 mesh) column chromatography (30% ethyl acetate in hexanes) to afford the desired product **42l** as pale-yellow liquid (35 mg, 40%).



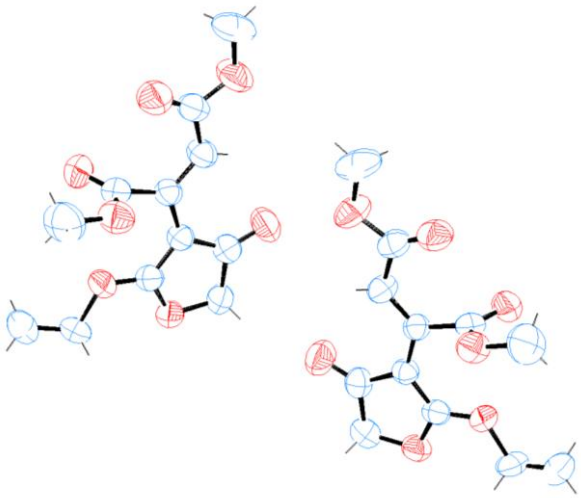
Analytical data of 42l

^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): δ 7.43 (d, *J* = 6.5 Hz, 2H), 7.38-7.35 (m, 3H), 6.62 (s, 1H) 5.26 (s, 2H), 4.83 (s, 2H), 4.43 (q, *J* = 7.0 Hz, 2H), 1.40 (t, *J* = 7.0 Hz, 3H)

^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ (ppm): 187.2, 174.5, 163.5, 161.8, 138.5, 134.4, 128.9, 128.7, 128.5, 114.8, 95.6, 62.5, 44.7, 14.0

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$calcd for $C_{17}H_{16}NO_5$: 314.1023; Found: 314.1023.

2.6.4 Single crystal X-ray of 40a



Single crystal X-ray of **40a** (CCDC: 2179228)

Crystal data and structure refinement for **40a**

Bond precision:	C-C = 0.0048 A		Wavelength=0.71073
Cell:	a=15.757(9)	b=7.301(6)	c=23.977(16)
	alpha=90	beta=107.46(2)	gamma=90
Temperature:	303 K		
	Calculated		Reported

Volume	2631(3)	2631(3)
Space group	P 21/c	P 21/c
Hall group	-P 2ybc	-P 2ybc
Moiety formula	C12 H14 O7	?
Sum formula	C12 H14 O7	C12 H14 O7
Mr	270.23	270.23
Dx,g cm-3	1.365	1.364
Z	8	8
Mu (mm-1)	0.114	0.114
F000	1136.0	1136.0
F000'	1136.79	
h,k,lmax	21,9,32	21,9,31
Nref	6602	6552
Tmin,Tmax	0.964,0.986	0.390,0.746
Tmin'	0.964	

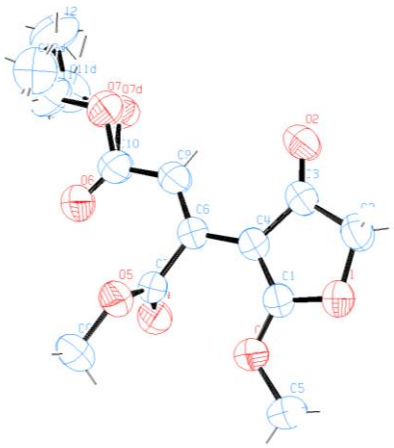
Correction method= # Reported T Limits: Tmin=0.390 Tmax=0.746 AbsCorr = MULTI-SCAN

Data completeness= 0.992 Theta(max)= 28.385

R(reflections)= 0.0676(2973) wR2(reflections)= 0.2492(6552)

S = 1.052 Npar= 350

2.6.5 Single crystal X-ray of 41a



Single crystal X-ray of **41a** (CCDC: 2179229)

Crystal data and structure refinement for **41a**

Bond precision: C-C = 0.0041 A Wavelength=0.71073

Cell:	a=8.072(7)	b=8.346(7)	c=11.666(9)
	alpha=100.03(2)	beta=106.34(2)	gamma=110.73(2)

Temperature: 301 K

	Calculated	Reported
Volume	671.7(10)	671.8(10)
Space group	P -1	P -1
Hall group	-P 1	-P 1
Moiety formula	C12 H14 O7	?
Sum formula	C12 H14 O7	C12 H14 O7
Mr	270.23	270.23
Dx,g cm-3	1.336	1.336
Z	2	2
Mu (mm-1)	0.111	0.111
F000	284.0	284.0
F000'	284.20	
h,k,lmax	9,10,14	9,9,13
Nref	2495	2177
Tmin,Tmax	0.986,0.989	0.448,0.745
Tmin'	0.986	

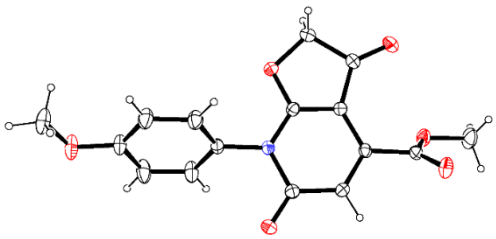
Correction method= # Reported T Limits: Tmin=0.448 Tmax=0.745 AbsCorr = MULTI-SCAN

Data completeness= 0.873 Theta(max)= 25.477

R(reflections)= 0.0489 (1551) wR2(reflections)= 0.1440 (2177)

S = 1.035 Npar= 203

2.6.6 Single crystal X-ray of 42c



Single crystal X-ray of **42c** (CCDC: 2178732)

Crystal data and structure refinement for **42c**

Identification code	shelx	
Empirical formula	C16 H13 N O6	
Formula weight	315.27	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21/c	
Unit cell dimensions	a = 14.1135(17) Å	α= 90°.
	b = 13.1113(17) Å	β= 103.152(4)°.
	c = 8.2694(11) Å	γ = 90°.
Volume	1490.1(3) $Å^3$	
Z	4	
Density (calculated)	1.405 Mg/m^3	
Absorption coefficient	0.109 mm^{-1}	
F(000)	656	
Crystal size	0.086 x 0.049 x 0.029 mm^3	
Theta range for data collection	2.964 to 25.999°.	
Index ranges	-17<=h<=16, -16<=k<=16, -6<=l<=10	
Reflections collected	16641	
Independent reflections	2931 [R(int) = 0.0745]	
Completeness to theta = 25.242°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.997 and 0.991	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2931 / 0 / 209	
Goodness-of-fit on F^2	1.012	
Final R indices [I>2sigma(I)]	R1 = 0.0496, wR2 = 0.1079	
R indices (all data)	R1 = 0.1176, wR2 = 0.1420	

Extinction coefficient	0.009(2)
Largest diff. peak and hole	0.202 and -0.153 e.Å^{-3}

2.7 References

1. J. C. Worch, C. J. Stubbs, M. J. Price, A. P. Dove, *Chemical Reviews,* **2021,** *121*, 12, 6744
2. M. M. Heravi, T. Alishiri, *Advances in Heterocyclic Chemistry*, Volume 113, ISSN 0065-2725
3. C. G. Neochoritis, T. Z. Tzitzikas, J. S. Stephanatou, *Synthesis*, **2014**, *46*, 0537.
4. H, Khabazzadeha, K, Saidia,H. Sheibania, M. R. Islamia, *Phosphorus, Sulfur Silicon Relat. Elem.*, **2007**, *182*, 2163.
5. A. Shaabani, E. Soleimani, H. R. Khavasi, R. D. Hoffmann, U. C. Rodewald, R. Pöttgen, *Tetrahedron Lett.*, **2006**, *47*, 5493.
6. J. Tae, K.O. Kim, *Tetrahedron Lett*., **2003**, *44*, 2125.
7. S. Murahashi, T. Naota, Y. Nakano, *Synlett*, **2009**, *20*, 3355
8. B. Léotard, T. Fukuyama, Y. Higashibeppu, C. Brancour, H. Okamoto, I. Ryu, *Synlett*, **2013**, 24, 2287.
9. W. Liu, C. Chen, Q. Zhang, *Synthetic Commu*., **2013**, *43*, 951.
10. Y. Xi, D. Wang, X. Ye, N. G. Akhmedov, J. L. Petersen, X, Shi, *Org. Lett*. **2014**, *16*, 306
11. H. Cao, H. Zhan, J. Cen, J. Lin, Y. Lin, Q. Zhu, M. Fu, H. Jiang, *Org. Lett.*, **2013**, *15*, 1080.
12. K. C. Brannock, R. D. Burpitt, V. W. Goodlett, J. G. Thweatt, *J. Org. Chem*. **1963**, *28*, 1464.
13. R. D. Clark, K. G. Untch, *J. Org. Chem*. **1979**, *44*, 253.
14. M. Miesch, F. Wendling, M. Franck-Neumann, *Tetrahedron Lett*. **1999**, *40*, 839.
15. Y. Shang, Y. C. Wu, Q. Gao, C. Liu, L. Li, X. Zhang, H. G. Cheng, S. Liu, Q. Zhou, *Nat. Commun.* **2021**, *12*, 2988.
16. H, G. Jessen, K. Gademann, *Nat. Prod. Rep.* **2010**, *27*, 1168.
17. Q. Li, L. A. Mitscher, L. L. Shen, *Med. Res. Rev*. **2000**, *20*, 231.
18. J. L. Medina-Franco, K. Martínez-Mayorga, C. Juárez-Gordiano, R. Castillo, *ChemMedChem,* **2007**, *2*, 1141.
19. P. Hong, H. Yamazaki, *Tetrahedron Lett.* **1977**, 1333.
20. H. Hoberg, B. W. Oster, *Synthesis*, **1982**, 324.

21. R. A. Earl, K. P. C. Vollhardt, *J. Org. Chem.* **1984**, 49, 4786.
22. Y. Yamamoto, K. Kinpara, T. Saigoku, H. Takagishi, S. Okuda, H. Nishiyama, K. Itoh, *J. am. chem. soc*. **2005**, *127*, 605.
23. H. A. Duong, M. J. Cross, J. Louie, *J. am. chem. soc*. **2004**, *126*, 11438.
24. R. T. Yu, T. Rovis, *j. am. chem. soc*. **2006**, *128*, 2782.
25. H. Imase, K. Noguchi, M. Hirano, K. Tanaka, *Org. Lett*., **2008**, 10, 3563.
26.
27. N. Guimond, S. I. Gorelsky, K. Fagnou, *J. am. chem. soc*. **2011**, *133*, 6449.
28. L. Ackermann, A. V. Lygin, N. Hofmann, *Org. Lett.* **2011**, *13*, 3278.
29. M. Fujii, T. Nishimura, T. Koshiba, S. Yokoshima, T. Fukuyama, *Org. Lett.* **2013**, *15*, 232
30. R. Manikandan, M. Jeganmohan, *Org. Lett.* **2014**, *16*, 3568.
31. S. Zhou, D. Y. Liu, S. Wang, J. S. Tian, T. P. Loh, *Chem. Commun.* **2020**, *56*, 15020
32. Z. Zhang, S. Fang, Q. Liu, G. Zhang, *J. Org. Chem.* **2012**, *77*, 7665
33. R. Ferraccioli, D. Carenzi, E. Motti, M. Catellani, *J. am. chem. soc.* **2006**, *128*, 722.
34. R. A. Mack, W. I. Zazulak, L. A. Radov, J. E. Baer, J. D. Stewart, P. H. Elzer, *J. Med. Chem.* **1988**,*31*, 1918
35. H. Y. Choi, D. Y. Chi, *Org. Lett.* **2003**, *5*, 411
36. V. Madhura, H. M. Revankar, M. V. Kulkarni, *J. Z. Naturforsch. B.* **2015**, *70*, 483
37. A. S. Patel, N. P. Kapuriya, Y. T. Naliapara, *J. Heterocyclic Chem.* **2017**, *54*, 2635
38. M. I. Ali, M. A. Abou-state, N. M. Hassan, *J. Chem. Eng. Data.* **1972**, *17*, 106
39. D. Brough, S. M. Allan, S. Freeman, A. G. Baldwin, U. S. Patent No: US 2018/0215772 Al, Aug. 2, **2018**.
40. B. Alexander, W. J. B. Reis, L. D. Alexander, M. Jonathan, S. Jean-Marie, M. William, WIPO, International Publication Number: WO 2013/002660 A2, Jan. 3, **2013**.

Chapter 3

Tandem *α*-Arylation/Cyclization of 4-Haloacetoacetates with Arynes: A Metal-Free Approach towards 4-Aryl-3-(2*H*)-Furanones

3.1 Introduction

Arynes are highly reactive intermediates and its enhanced reactivity could be attributed to its low-lying lowest unoccupied molecular orbital (LUMO) and strain energy of 63 kcal mol^{-1}. The first report on the existence of such a transient species was made by Stoermer and Kahlert in 1902. But due to the transient nature, its characterization and development as a potential synthon in organic chemistry emerged only recently. The next benchmark in aryne chemistry was realized in 1942 when Wittig proposed arynes as intermediates in the reaction of fluorobenzene with phenyllithium. Finally, In 1953 Roberts *et. al.* confirmed the structure by ^{14}C labelling experiment of ^{14}C-chlorobenzene with potassium amide.[1,2,3]

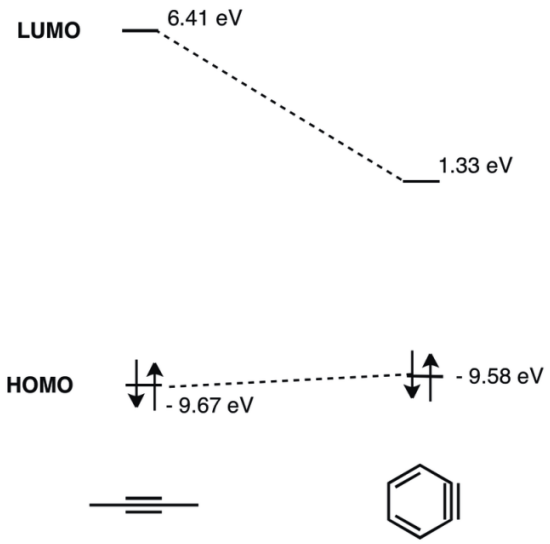


Fig 3.1. HOMO-LUMO energy differences in dimethyl acetylene and benzyne.

Benzyne have a strained triple bond and the second π-bond in benzyne is formed by the overlap of unhybridized p-orbitals, and it is perpendicular to the initially formed one. Due to this distorted geometry, they are no longer parallel to each other as in normal alkynes. When we compare the triple bond characteristics of benzyne with alkyne, experimental evidences show that the C—C triple bond length in benzyne (122-126 pm) is closer to that of alkyne (120.3 pm) than ethylene (133 pm). The IR peak in benzyne is at 1846 cm^{-1}, while in an unstrained alkyne it has the stretching vibrations at about 2150 cm^{-1}. This clearly indicates its weaker characteristics as a strained alkyne. The enthalpy of formation is reported as 103.6–

109.6 kcal mol^{-1} and its ^{13}C value of 182 ppm also explains its strained alkyne character. The high electrophilicity of arynes can be explained on the basis of its significantly lower LUMO compared to dimethyl acetylene (5.1 eV). It has also been observed that the HOMO is also higher (0.1 eV) in energy, which make the aryne triple bond much more accessible for different nucleophiles.[1,2]

3.2 Generation of arynes

Different groups have reported various approaches for the generation of this highly reactive intermediate and due to the high reactivity, arynes are generated *in-situ* in solution and cannot be isolated. The conventional method includes the deprotonation of aryl halides followed by the dehalogenation of the anionic intermediate with strong bases such as sodamide or n-BuLi (Fig 3.2). But the practical application of this method is limited due to base-sensitive functional group intolerance and requirement of harsh reaction conditions for the generation of arynes.

Another method reported in literature is the metal–halogen exchange/elimination of 1,2-disubstituted haloarenes or haloaryl triflates. The reaction proceeds *via* the metal-halogen exchange or elimination reaction (Mg or Li or organometallic reagents derived from Cu, Li, and Mg). But the competitive reactions of the nucleophilic addition of the organometallic reagents itself have made this route less practical.

The decomposition of benzenediazonium 2-carboxylate upon heating with the elimination of nitrogen and carbon dioxide is another strategy reported for benzyne generation. The zwitterionic benzenediazonium-2-carboxylates generated from anthranilic acid derivatives *via* Sandmeyer's condition. But the explosive nature of diazonium compounds limits the practical application of this method.

Another method includes the fragmentation of benzo[*d*][1,2,3]thiadiazole 1,1-dioxide and amino benzotriazoles using lead tetraacetate with the liberation of nitrogen gas. The disadvantages associated with this method includes the use of explosive precursor, low functional group tolerance and the requirement of lead tetraacetate as oxidant.[1,2,3,8,9]

The widely accepted route towards the generation of benzyne was reported by Kobayashi and coworkers in 1983. They developed a mild and base free protocol for the generation of arynes from 2-(trimethylsilyl)aryl triflates. It involved a fluoride ion induced 1,2-elimination of 2-(trimethylsilyl)aryl triflates to generate arynes in solution.[10] This method is considered as a breakthrough in the development of aryne chemistry. The wider acceptance of this method is due to its compatibility with a range of functional groups and reagents. The common fluoride

sources used in this method are KF (with 18-crown-6 as additive) in THF, CsF in CH_3CN, TBAT in THF, and tetrabutyl ammonium fluoride (TBAF) in THF. This method has additional advantages which includes, the control of reaction rate with the kinetics of aryne generation from the 2-(trimethylsilyl)aryl triflates through the selection of fluoride source and solvent combination.[11]

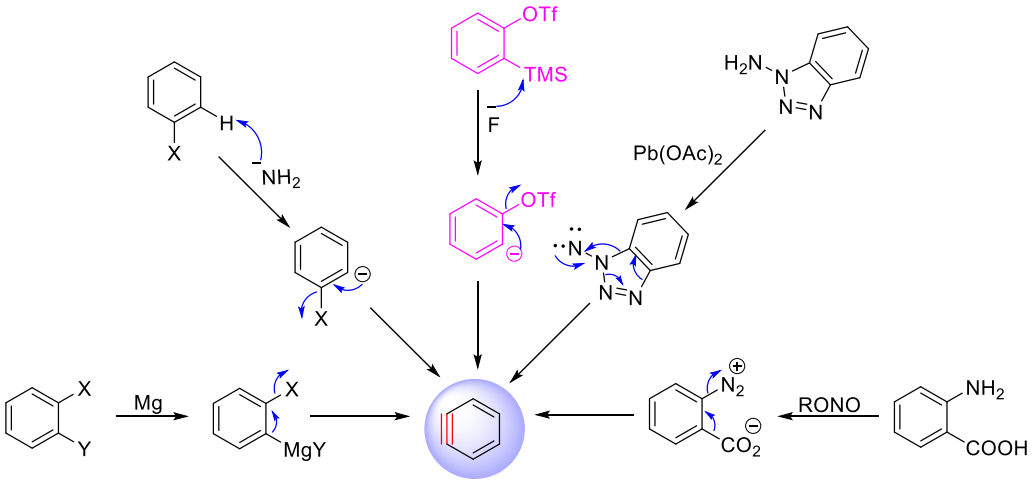


Fig 3.2. Different approaches for the generation of arynes.

Kobayishi's method hold a superior position over the other methods reported in literature due to its easiness in handling, functional group tolerance and less toxicity. After establishment of this method, an exponential rise was observed in the chemistry of benzynes. Many reactions were re-investigated with Kobayishi's method of aryne generation and many of them resulted in better conversions than previous reports.

3.3 Reactivity of arynes

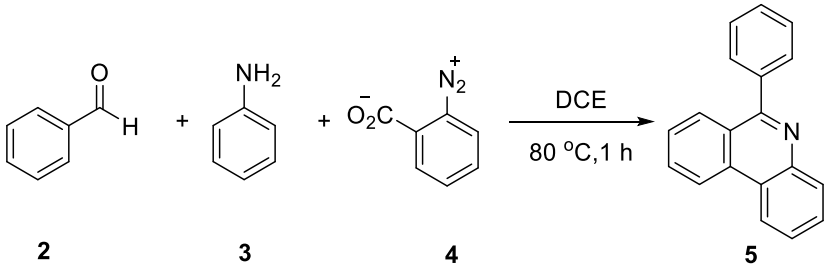
As mentioned above, the success of aryne chemistry in organic synthesis can be attributed to their low-lying LUMO and strained triple bond. Because of its high reactivity, its chemistry as electrophiles is unparallel. The pronounced electrophilicity of arynes render them as excellent dienophiles in pericyclic reactions such as Diels–Alder reactions, [2+2] cycloaddition reactions, dipolar cycloaddition reactions etc. In addition, arynes have been extensively utilized in multicomponent reactions, arylation and insertion reactions.

3.3.1. Pericyclic reactions

One of the most studied reactions exhibited by benzyne is the Diels–Alder reaction. This reaction is considered as a versatile pathway for the construction of substituted carbocycles and heterocycles. Along with this, benzynes are also recognized as excellent dienophiles and

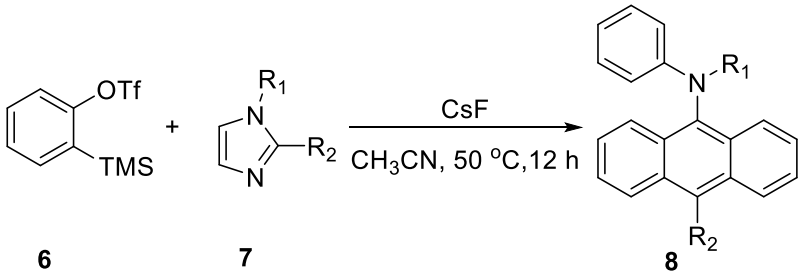
dipolarophiles in [2+2] and [3+2] cycloaddition reactions respectively. Representative examples of cycloadditions of benzyne are listed below.

In 2006, Wang and co-workers reported a three-component reaction of arynes (generated from the benzenediazonium-2-carboxylates) and imines generated from aromatic aldehydes and aniline derivatives *via* an aza Diels–Alder pathway. The synthesis resulted in the formation of phenanthridine derivatives (Scheme 3.1).[12]



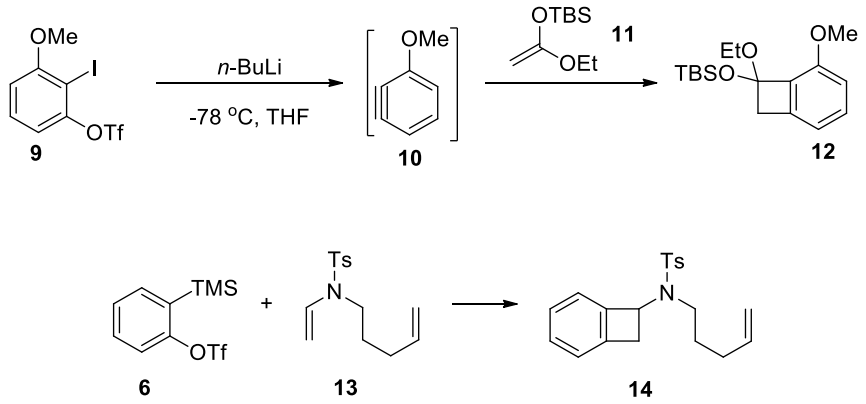
Scheme 3.1

Later, Zhang *et.al* reported the synthesis of aryl amine incorporated anthracene from the reaction of arynes with *N*-substituted imidazoles **7**. The reaction proceeds *via* Diels–Alder reaction and an intermolecular coupling reaction (Scheme 3.2).[13]



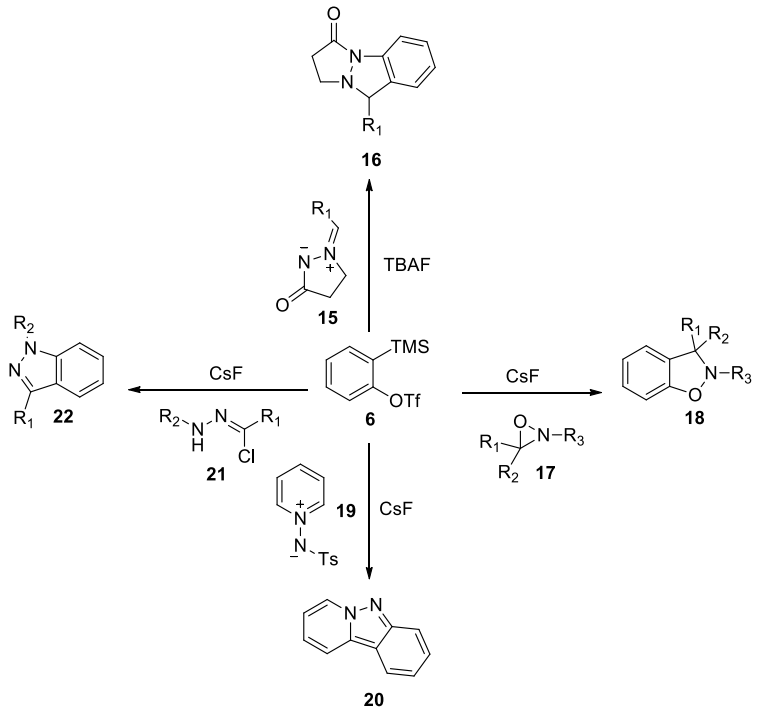
Scheme 3.2

Arynes can participate in [2+2] cycloaddition reactions with a range of olefins for the generation of benzocyclobutane derivatives, a class of useful synthetic intermediates. Due to the electrophilic nature of arynes, these reactions proceed faster with alkenes containing electron-donating substituents. In 2002, Suzuki and co-workers reported the regioselective [2+2] cycloaddition of 3-methoxybenzyne **9** with ketene silyl acetal **11**. The high regioselectivity in the cyclobutane ring formation is associated with the stabilization of arynes due to the presence of methoxy group on the aryne precursor (Scheme 3.3).[14,15]



Scheme 3.3

Benzyne can act as a dienophile with 1,3-dipoles in a [3+2] cycloaddition reaction for the synthesis of benzofused five-membered heterocyclic systems. Larock and co-workers in 2009 established a [3+2] cycloaddition between azomethine imines **15** and arynes under mild reaction conditions for the generation of tricyclic pyrazoloindazolone derivatives **16** (Scheme 3.4).[16] After this, various groups have developed protocols for the [3+2] cycloaddition of various 1, 3-dipoles with benzynes. These include the facile dipolar cycloaddition of oxaziridines **17** with arynes *via* the cleavage of the C–O bond of oxaziridine for the synthesis of dihydrobenzisoxazoles **18**,[17] nitrile imines with benzyne for the generation of indazole and *N*-tosylpyridinium imides **19** with benzyne for pyridoindazole **20** (Scheme 3.4).[18,19]

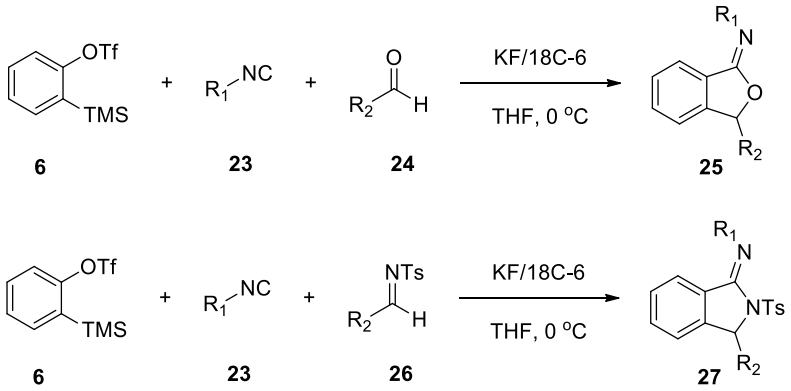


Scheme 3.4

3.3.2. Multicomponent reactions

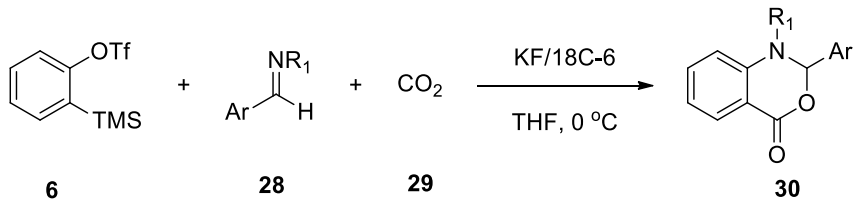
Another interesting chemistry reported with aryne is its reactivity in multicomponent reactions. The reaction is initiated with the attack of nucleophile to the aryne resulting in the formation of an anion, which was trapped by an electrophile to give a 1,2-diustituted arene. It becomes a three-component reaction, if the electrophiles and nucleophiles are derived from two molecules.

In 2004, Yoshida and co-workers developed a three-component reaction of arynes **6** with isocyanides **23** and aldehydes **24** for the generation of benzannulated iminofurans **25** in good yields (Scheme 3.5). The reaction was initiated by the nucleophilic addition of isocyanide to aryne to form the 1,3-zwitterionic intermediate, which was trapped by the aldehyde, and a subsequent intramolecular cyclization furnished the product **25**. Further studies revealed that the reaction is not only limited to aldehydes as the electrophilic component, but also for activated imines, ketones and benzoquinones as the third component.[20,21]



Scheme 3.5

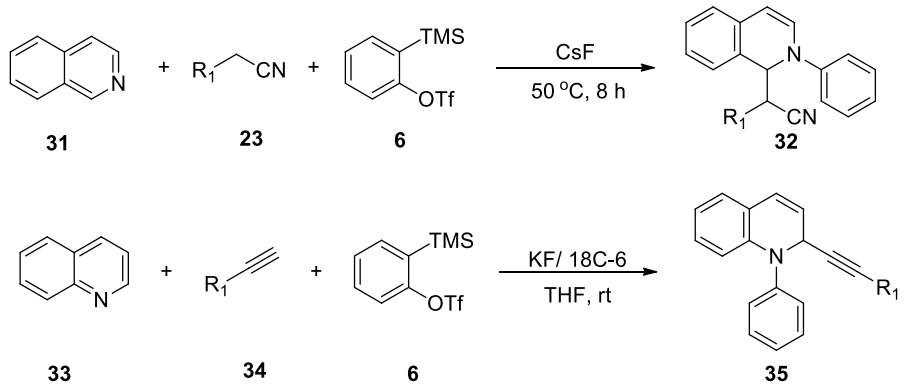
In another piece of work, the same group used CO_2 as the third coupling partner and the zwitterion generated by the addition of imines **28** to arynes was trapped with CO_2 for the formation of pharmacologically important benzoxazinone derivatives **30** (Scheme 3.6).[22]



Scheme 3.6

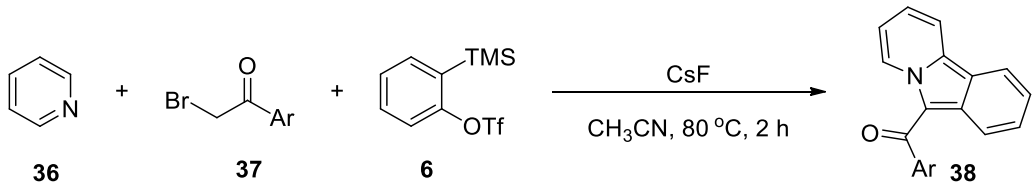
Cheng and co-workers reported the multicomponent reaction of arynes, *N*-heteroaromatic compounds with terminal alkynes or nitriles having α-hydrogen atoms. When nitriles are used

as the third component, this method allows the one-pot formation of new C–C and C–N bonds, while with alkyne as the third component, it gave 1,2-dihydroaromatic alkynes (Scheme 3.7).[23,24]



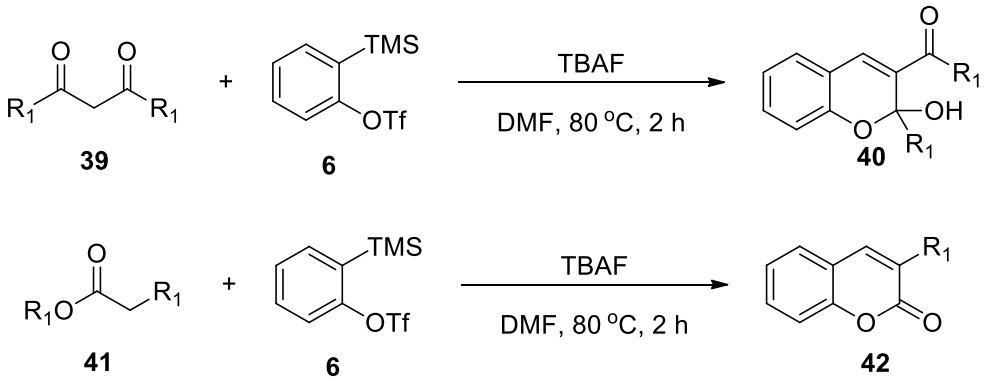
Scheme 3.7

In 2008, another multicomponent reaction involving arynes, pyridine **36** and an *α*-bromo carbonyl compound **37** was reported by Zhang and Huang independently. The reaction afforded the fused pyrido[2,1-*a*]isoindoles **38** as the product (Scheme 3.8). The reaction was initiated with the formation of the pyridinium salt which generates the azomethine ylide and subsequent [3+2] cycloaddition with the aryne followed by aromatization afforded the product.[25]



Scheme 3.8

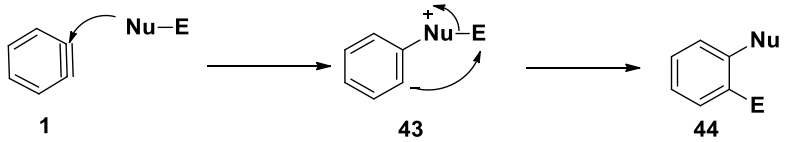
Miyabe and Yoshida independently reported the three-component reaction between aryne, dimethyl formamide (DMF) and an active methylene compound **39** or **41**. The reaction proceeded *via* the formation of an *o*-quinone methides from aryne and DMF, which upon insertion with the 1,3-dicarbonyl compounds afforded the 2*H*-chromenes **40** and coumarin derivatives **42**, respectively with **39** and **41** (Scheme 3.9).[26,27]



Scheme 3.9

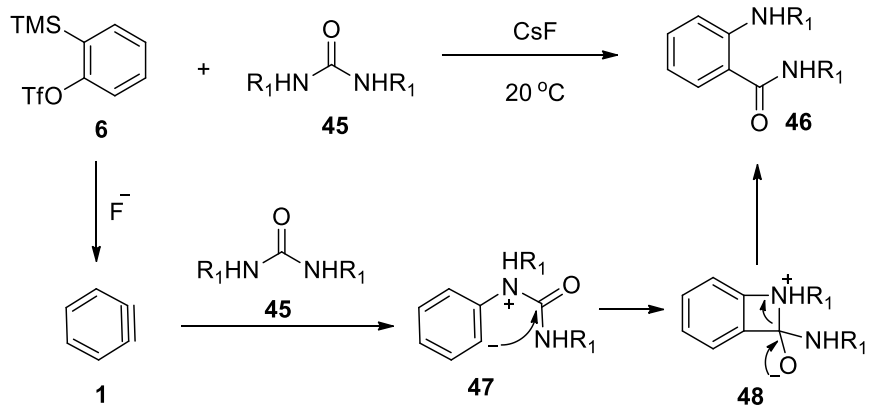
3.3.3 Insertion reactions

Another important transformation that arynes are susceptible to is insertion reactions with element–element bonds. Since arynes are highly electrophilic compounds, they are easily accessible to nucleophiles, for the *in-situ* generation of aryl anions. As a result, they are extensively employed for the synthesis of functionalized 1,2-disubstituted arenes. While comparing with multicomponent reactions, here the nucleophilic and electrophilic sites are normally seen in a single moiety (Nu–E). The initially formed zwitterion undergoes nucleophilic attack on the electrophilic site of Nu–E to form the insertion product.



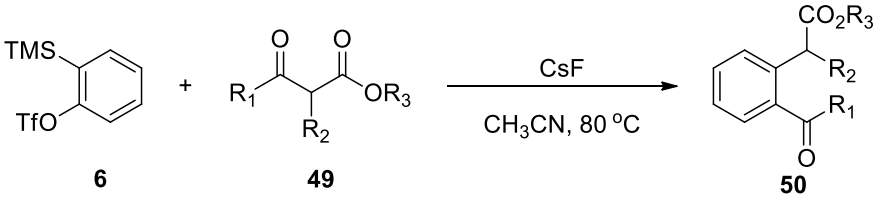
Scheme 3.10

The first report on the insertion chemistry of arynes was reported by Hiyama and co-workers in 2002. They observed the addition of urea to arynes leading to the formation of 2-aminobenzamides **46**. The reaction proceeded *via* the insertion of arynes into the N–CO bond of urea, which resulted in the generation of zwitterion intermediate **47** which upon intramolecular nucleophilic substitution with the amide carbonyl followed by 4-membered ring rupture afforded the 1,2-disubstituted arene **46** (Scheme 3.11).[28]



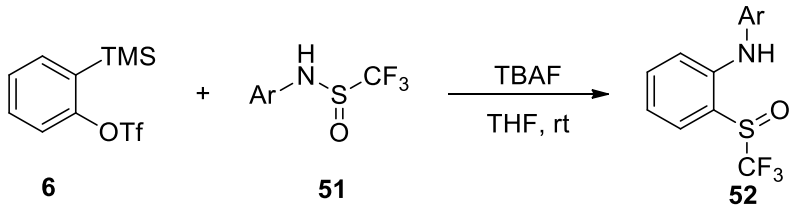
Scheme 3.11

Later, Stoltz *et. al.* developed a protocol for the insertion of 1,3-dicarbonyl compounds with arynes. The reaction resulted in the formation of two new C–C bonds by the insertion of arynes into the *α, β*-C–C bond of the *β*-ketoester (Scheme 3.12).[29] Later, they have utilized the developed methodology for the enantioselective synthesis of amurensinine, an isopavine belonging to the family of alkaloids.



Scheme 3.12

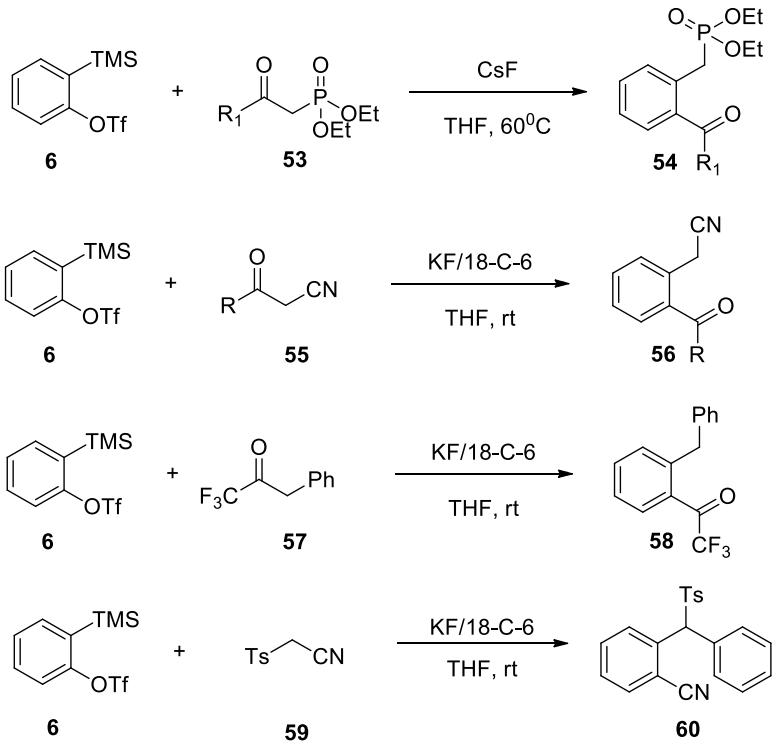
Larock developed a mild reaction pathway for the insertion of arynes into the C–N bond of amides and the S–N bond of sulfonamides (Scheme 3.13). In this reaction they observed that the CF_3 moiety has two functions, first one is to increase the acidity of the amide and the other one is to increase the electrophilicity of the sulfinyl sulfur of the sulfonamide for insertion reaction.[30]



Scheme 3.13

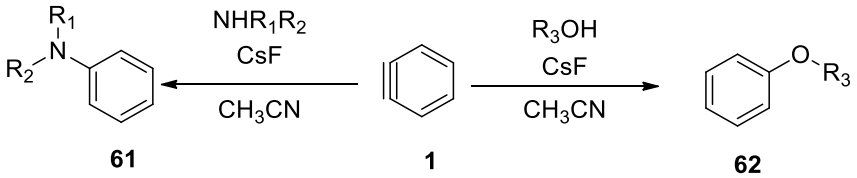
After establishing successful strategies for the insertion of *β*-dicarbonyl compounds in arynes, various protocols were reported in literature for the insertion of *α*-cyanocarbonyl

compounds **55**, *α*-tosylnitriles **59**, *β*-ketophosphonates **53**, trifluoromethyl ketones **57** etc. into arynes under milder reaction condition (Scheme 3.14).[31-34]

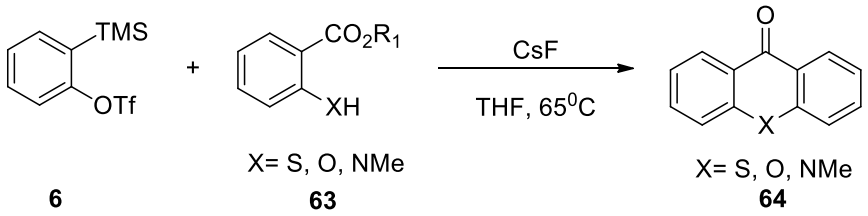


Scheme 3.14

Larock *et. al* developed an efficient, mild and transition-metal-free method for the *N*-or *O*-arylation by the insertion of arynes into the N–H bond of amines and O–H bond of alcohols (Scheme 3.15). The reaction can afford monoarylated and diarylated amines from primary amines by the simple control of the ratio of reactants. [35,36] This methodology was later used by the same group for the synthesis of biologically interesting xanthone **64** derivatives by a tandem insertion– cyclization sequence of arynes with 2-substituted benzoates (Scheme 3.16).[37]



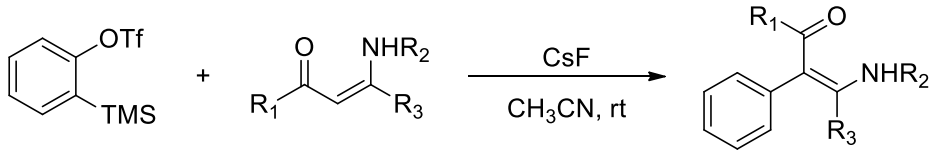
Scheme 3.15



6 **63** **64**

Scheme 3.16

Later, in 2006 another *C*-arylation chemistry was reported with *β*-enaminoesters and ketones **65** *via* the usual insertion of arynes into the *β*-C–H bond. This work provided a direct access to substituted aromatic *β*-enamino compounds. The reaction initiated with the addition of enaminones to arynes generated a zwitterionic intermediate, which upon protonation and subsequent tautomerization afforded the *β*-enamino compounds **66 (**Scheme 3.17).[38]



6 **65** **66**

Scheme 3.17

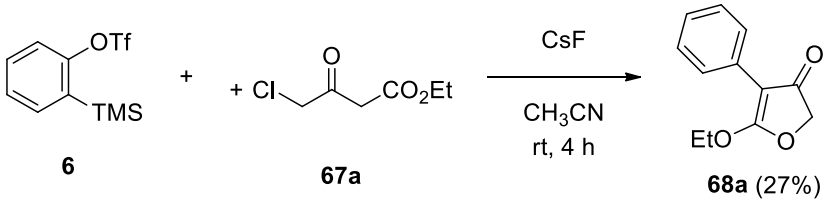
3.4. Statement of the problem

In this chapter, we describe our efforts on the development of a metal free tandem reaction for the synthesis of 4-aryl-3(2*H*)-furanones from simple and easily available starting materials such as 4-halo-1,3-dicarbonyl compounds and benzynes. Chemically, benzyne shows the properties of a highly reactive alkyne, participating in a range of cycloaddition, multicomponent, arylation and insertion reactions. It also resembles a carbene, having the similar electronic arrangement of two electrons distributed between two orbitals and behaves as a powerful electrophile. Due to the inherent electrophilicity of benzynes, synthetic organic chemists are wisely using this intermediate for trapping various nucleophiles. In literature, the biological significance and synthetic utilization of 3-(2*H*)-furanones are an interesting topic of research. Among substituted 3-(2*H*)-furanones, aryl-furanones have a distinct position due to their wide range of biological applications and especially its selective cox-2 inhibition.

3.5 Results and Discussion

We initiated the investigations with 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **6** and ethyl 4-chloroacetoacetate **67a** as substrates. The first reaction of **6** with **67** was performed in the presence of 5.0 equivalents of CsF (which is the F^- source for the generation of benzyne

and also a base) in CH_3CN at room temperature (Scheme 3.18). As expected, 4-phenyl-3-(2*H*)-furanone **68a** was isolated from the reaction in 27% yield after 4 h. The structure of **68a** was assigned based on ^{1}H NMR, ^{13}C NMR, 2-D NMR, high resolution mass spectral analyses.



Scheme 3.18

In the ^{1}H NMR spectra (Fig 3.3), the aromatic protons were found to resonate in between 7.80-7.12 ppm. The methylene proton in the furanone ring was found to be at 4.48 ppm as a singlet and the methylene protons in the ethoxy group resonated at 4.54 ppm. The methyl protons in the ethoxy group resonated as a triplet at 1.45 ppm. In the ^{13}C NMR spectrum (Fig 3.4), the furanone carbonyl resonated at 194.1 ppm and the C5 carbon resonated at 180.6 ppm. The C2 methylene carbon found at 74.6 ppm and the aromatic carbons were found to be resonated in between 129.4 to 125.9 ppm. All other signals in the ^{13}C NMR spectra were in agreement with the proposed structure. The high resolution mass spectral analysis showed a peak at *m/z* 204.0797 $(M+Na)^+$, which also supported the proposed structure. The structure of the product was further supported with the single crystal X-ray analysis of compound **68a** and the ORTEP diagram (Fig 3.5) of the same is shown below.

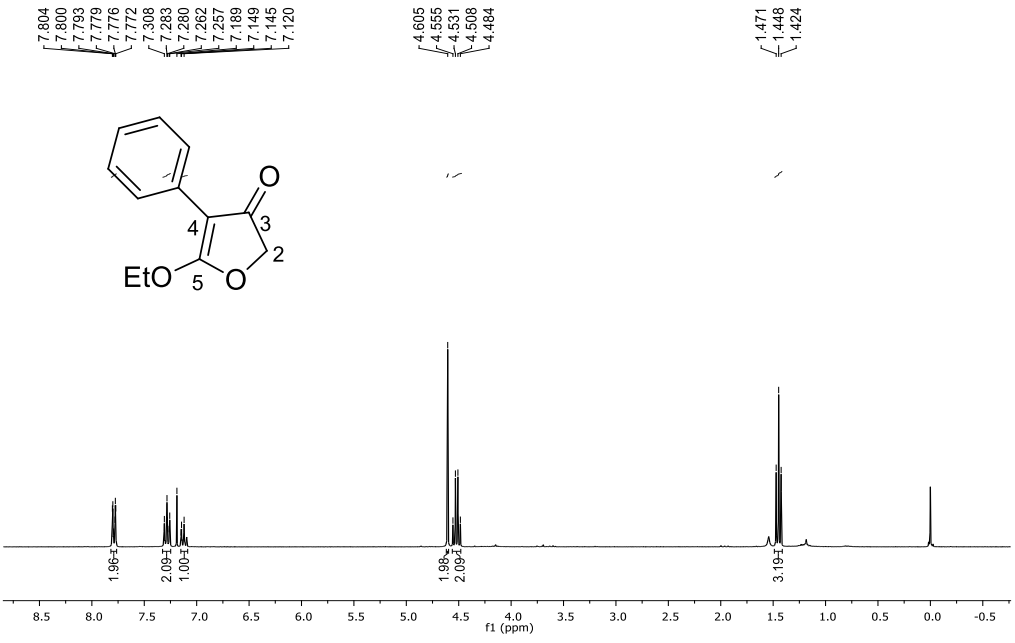


Fig 3.3. ^{1}H NMR spectrum of compound **68a**.

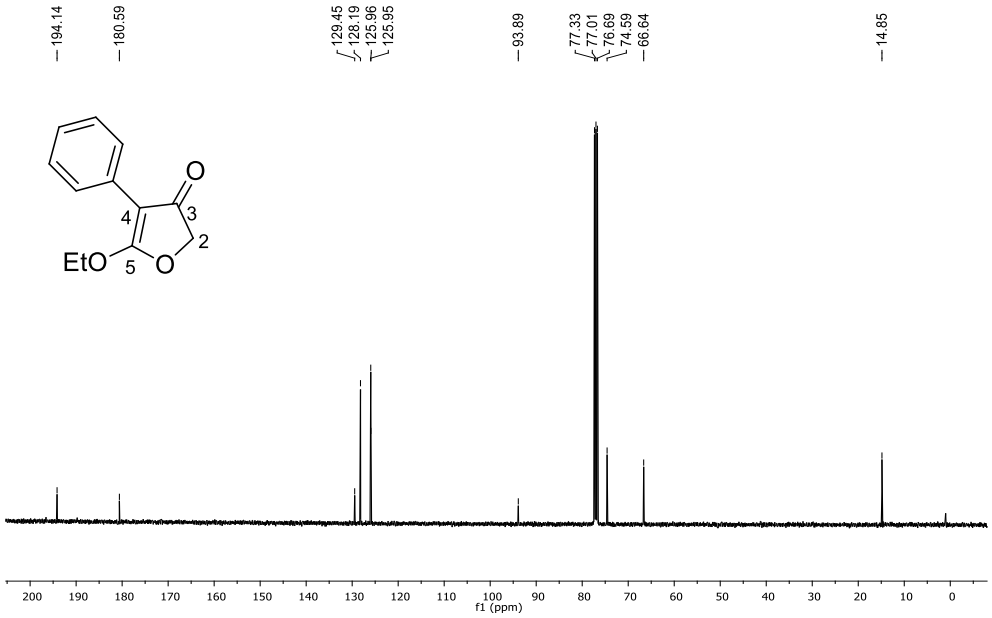


Fig 3.4. ^{13}C NMR spectrum of compound **68a**.

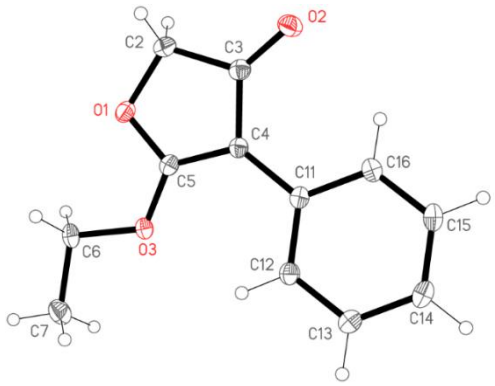
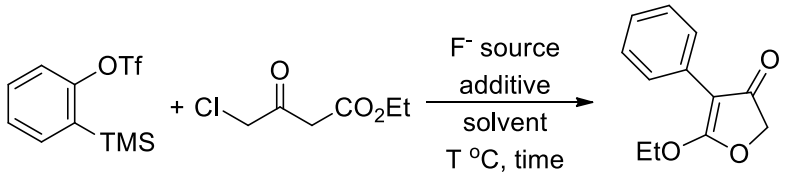


Fig 3.5. Single crystal X-ray of **68a**. (CCDC-1891729)

Our optimization studies with **6** and **67a** commenced with the screening of F^- sources such as CsF, KF/18C-6 and TBAF; the combination of KF/18C-6 afforded 4-phenyl-3(2*H*)-furanone in the highest yield (entries 1-3). We then checked the efficacy of different additives such as K_2CO_3, Na_2CO_3 and $NaHCO_3$ (entries 4-6). These reactions were performed with 3.0 equivalents of KF/18C-6 and 2 equivalents of the additive. Disappointingly, none of the reactions with additives resulted in yield improvement. Next, we screened different solvents such as CH_3CN, THF, DMF, DME and 1,4-dioxane. From the solvent optimization, CH_3CN was found afford **68a** in the best yield (entries 2, 7-10). A slight improvement in the yield of 4-phenyl-3-(2*H*)-furanone was observed by increasing the amount of benzyne precursor **6** to 1.25

equivalents (entry 11). Finally, we studied the effect of temperature on the outcome of the reaction. For this we started the reaction at 0 ºC and allowed the reaction mixture to attain ambient temperature gradually; from this reaction the expected furanone **68a** was isolated in 70 % yield (entry 12). Thus, the optimized conditions for the reaction were found to be a combination of 1.25 equivalents of benzyne precursor, 1.0 equivalent of 4-haloacetoacetate, 5.0 equivalents of KF/18C-6 in CH_3CN at 0 ºC, and subsequent stirring at room temperature for 5 h.

Table 3.1. Optimization studies



6 **67a** **68a**

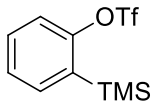
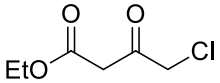
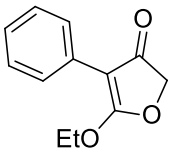
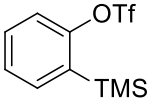
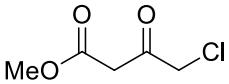
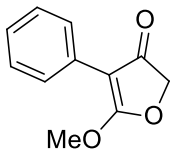
Entry	F^- source	Additive	Solvent	Yield of **68a** (%)[a]
1	CsF	-	CH_3CN	27
2	KF/18C-6	-	CH_3CN	51
3	TBAF	-	CH_3CN	46
4	KF/18C-6	K_2CO_3	CH_3CN	43[b]
5	KF/18C-6	Na_2CO_3	CH_3CN	32[b]
6	KF/18C-6	$NaHCO_3$	CH_3CN	21[b]
7	KF/18C-6	-	THF	36
8	KF/18C-6	-	DMF	16
9	KF/18C-6	-	DME	43
10	KF/18C-6	-	1,4-dioxane	46
11	KF/18C-6	-	CH_3CN	61[c]
12	**KF/18C-6**	-	**CH_3CN**	**70[d]**

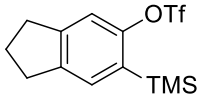
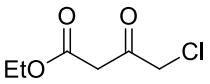
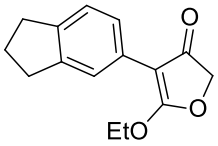
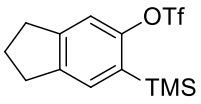
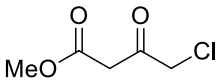
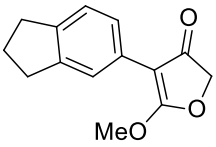
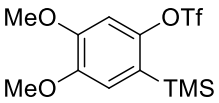
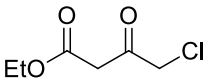
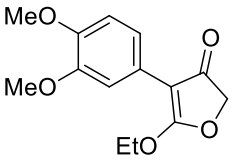
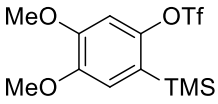
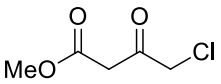
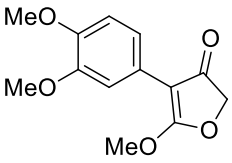
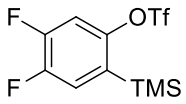
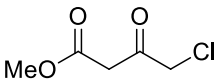
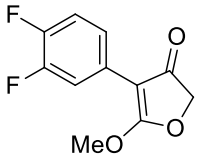
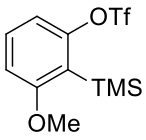
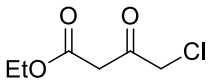
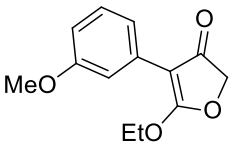
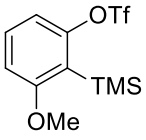
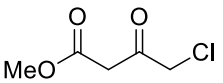
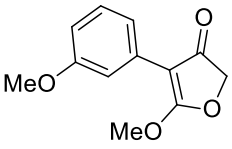
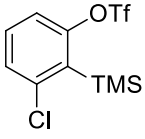
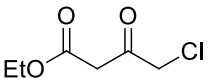
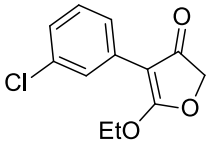
[a]Reaction conditions: **6** (1.0 equiv., 0.6 mmol), **67a** (1.0 equiv., 0.6 mmol), F^- source (5.0 equiv.), solvent (4.0 mL), rt, 4 h, isolated yield. [b] F^- source (3.0 equiv.), additive (2.0 equiv.). [c] **6** (1.25 equiv.), **67a** (1.0equiv.). [d] 0 ºC - rt, 5 h.

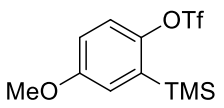
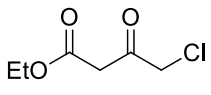
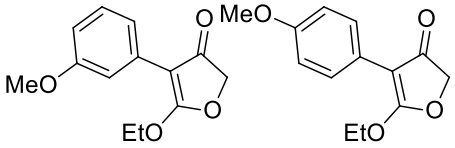
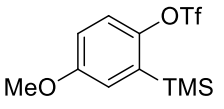
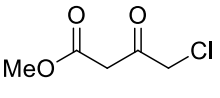
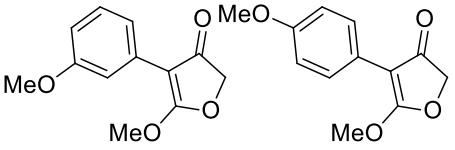
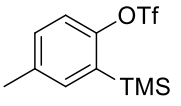
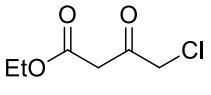
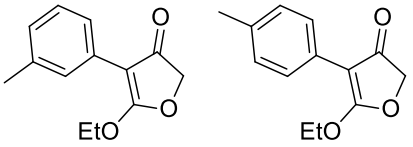
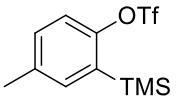
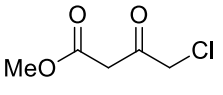
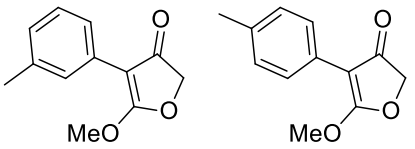
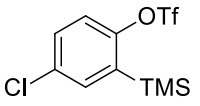
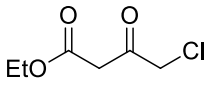
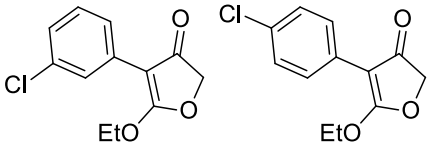
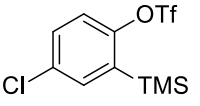
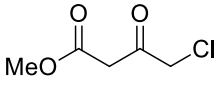
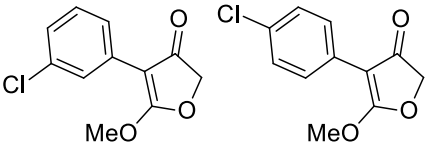
These optimized conditions for the tandem *a*-arylation/cyclization methodology was utilized for studying the generality of differently substituted arynes (Table 3.2). Both ethyl **67**

and methyl acetoacetates **67b** participated in the cascade reaction with simple benzyne affording the corresponding 4-phenyl-furanones **68a** and **68b** in 70% and 73% yields respectively. The compound **68b** was also made on the gram scale and that too in good yields (69%). The reactions of **67a** and **67b** with 6-(trimethylsilyl)-2,3-dihydro-1*H*-inden-5-yl triflate **6b** afforded the expected products **68c** and **68d** in good yields. Disubstituted aryne precursors such as 4,5-dimethoxy-*ortho*-silylphenyltriflate and 4,5-difluoro-*ortho*-silylphenyltriflate also participated in the tandem reaction with 4-haloacetoacetates furnishing the 4-arylated furanones **68e-g** in moderate to good yields. Importantly, the reaction of 4,5-difluoro-*ortho*-silylphenyltriflate was found to be complete in 2 h at 0 ^{o}C. Interestingly, the fluoride-induced tandem reaction of 3-methoxy-1,2-benzyne with **67a** and **67b** afforded furanones **68h and 68i** as single regioisomers and in good yields. High regiospecificity was also observed in the reaction between 3-chloro-1,2-benzyne and ethyl-4-chloroacetoacetate **67a** wherein the product **68j** was isolated in 61% yield. Nevertheless, the reactions of some other 4-substituted-1,2-benzynes with 4-chloroacetoacetates afforded an inseparable mixture of regioisomers. In the case of 4-methoxybenzyne the products **68k** and **68l** were obtained as a mixture of regioisomers in the ratios 1:1.3 and 1:1.8 respectively. Whereas, the reactions of **67a** and **67b** with 4-methyl benzyne afforded the products **68m** and **68n** in good yields but as 1:1 regioisomeric mixtures. The reactions of 4-chloro benzyne with **67a** and **67b** also afforded the corresponding substituted furanones **68o-p** as mixtures of regioisomers and in slightly lower yields than the former.

Table 2.2. Generality of 4-aryl-3-(2*H*)-furanone synthesis with various arynes

Entry	Arynes	4-Halo-1,3-dicarbonyl compounds	Product	Yield (%)
1	 **6**	 **67a**	 **68a**	70
2	 **6**	 **67b**	 **68b**	73

3	 **6b**	 **67a**	 **68c**	67
4	 **6b**	 **67b**	 **68d**	68
5	 **6c**	 **67a**	 **68e**	67
6	 **6c**	 **67b**	 **68f**	68
7	 **6d**	 **67b**	 **68g**	48
8	 **6e**	 **67a**	 **68h**	71
9	 **6e**	 **67b**	 **68i**	73
10	 **6f**	 **67a**	 **68j**	61

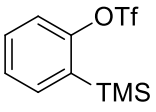
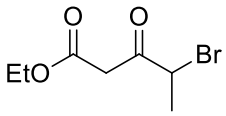
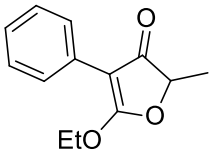
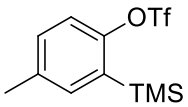
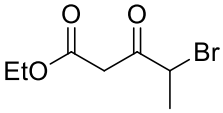
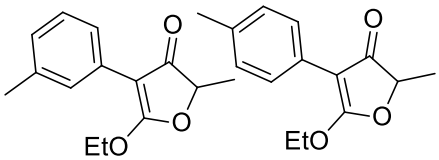
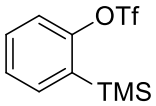
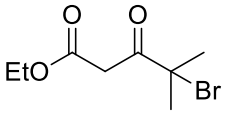
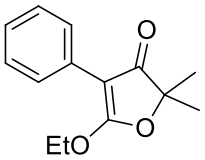
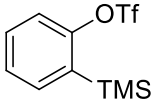
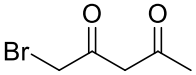
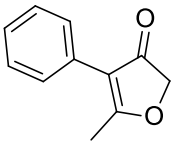
11	 **6g**	 **67a**	 **68k** (1.0: 1.3)	67
12	 **6g**	 **67b**	 **68l** (1.0: 1.8)	70
13	 **6h**	 **67a**	 **68m** (1.0: 1.0)	71
14	 **6h**	 **67b**	 **68n** (1.0: 1.0)	75
15	 **6i**	 **67a**	 **68o** (1.0: 1.2)	62
16	 **6i**	 **67b**	 **68p** (1.0: 1.4)	66

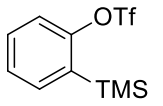
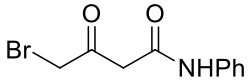
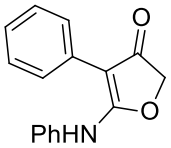
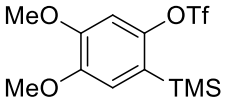
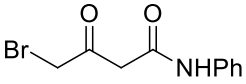
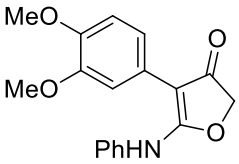
Reaction conditions: **6** (1.25 equiv.), **67a** (1.0 equiv.), KF (5.0 equiv.), 18C-6 (5.0 equiv.), CH_3CN (4.0 mL), 0 ^oC-rt, 5 h. [a]started with 1.0 gm of **67b**, [b]0 ^oC, 2 h. [c]0 ^oC, 4 h.

We then turned our attention in bringing variations to the 4-haloacetoacetate part and thereby chose ethyl 4-bromo-3-oxopentanoate **67c** with the idea of introducing a methyl group at the second position of the 3(2*H*)-furanone moiety (Table 3.3). The reaction was found to work well with simple benzyne which afforded the 2-methyl-4-phenyl-3(2*H*)-furanone **68q** in

69% yield. A 1.2:1 regioisomeric mixture of substituted furanones **68r** was obtained in good yield by the reaction of **67c** with 4-methyl benzyne. However, our attempt to introduce two methyl groups at the second position of 3(2*H*)-furanone with ethyl 4-bromo-4-methyl-3-oxopentanoate **67d** was unsuccessful (intractable reaction mixture) even on heating. Our next effort was to check the reactivity of 4-bromo-3-oxo-*N*-phenylbutanamide **67e** toward the present tandem reaction. The reactions with unsubstituted benzyne (**6**) and dimethoxybenzyne (**6c**) afforded substituted furanones **68u and 687v** in moderate yields. To our dismay, the reaction of 1-bromopentane-2,4-dione **67d** failed to furnish the expected product **68t** under the optimized conditions.

Table 3.3. Generality of 4-aryl-3-(2*H*)-furanone synthesis with various 4-haloacetoacates

Entry	Arynes	4-Halo-1,3-dicarbonyl compounds	Product	Yield (%)
1	 **6**	 **67c**	 **68q**	69
2	 **6h**	 **67c**	 **68r** (1.2: 1.0)	63
3	 **6**	 **67c**	 **68s**	Not isolated
4	 **6**	 **67d**	 **68t**	Not isolated

5	 **6**	 **67e**	 **68u**	52
6	 **6c**	 **67e**	 **68v**	48

Reaction conditions: **6** (1.25 equiv.), **67** (1.0 equiv.), KF (5.0 equiv.), 18C-6 (5.0 equiv.), CH_3CN (4.0 mL), 0 ^oC-rt, 5 h. [a] 60 ^oC, 6 h.

A plausible mechanism for the formation of 4-aryl-3-(2*H*)-furanone (Figure 3.5) is computed using M06L/SMD/6-311G(d,p) level density functional theory (SI). The fluoride-induced formation of enolate (**a** to **b** *via* **TS1**) is nearly barrier-less and the subsequent formation of the anionic benzyne adduct **c** is spontaneous and highly exothermic. Similarly, the proton abstraction from HF by the aryl anion **c** has to take place instantaneously due to the formation of the highly exothermic product **d**, the arylated ester-flouride ion complex. At this stage, F^- anion abstracts the proton from the remaining C-H bond to form the arylatedenolate-HF complex (**e**). The transition state **TS2** for this reaction suggests the barrier height 4.0 kcal/mol. The enolate **f** undergoes an intramolecular cyclisation through the formation of an S_N2 type transition state **TS3** to yield the final product in association with the leaving group Cl^-(**g**). The activation barrier for the cyclisation is 13.1 kcal/mol and the exothermic character of the overall reaction is 102.0 kcal/mol.

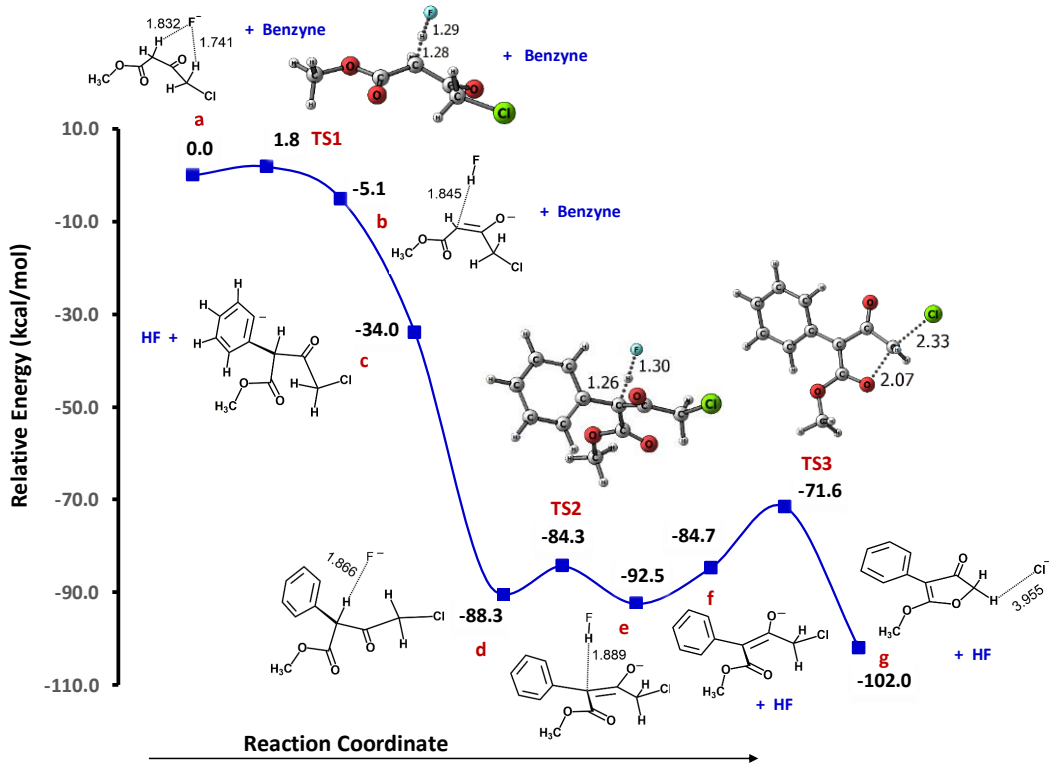
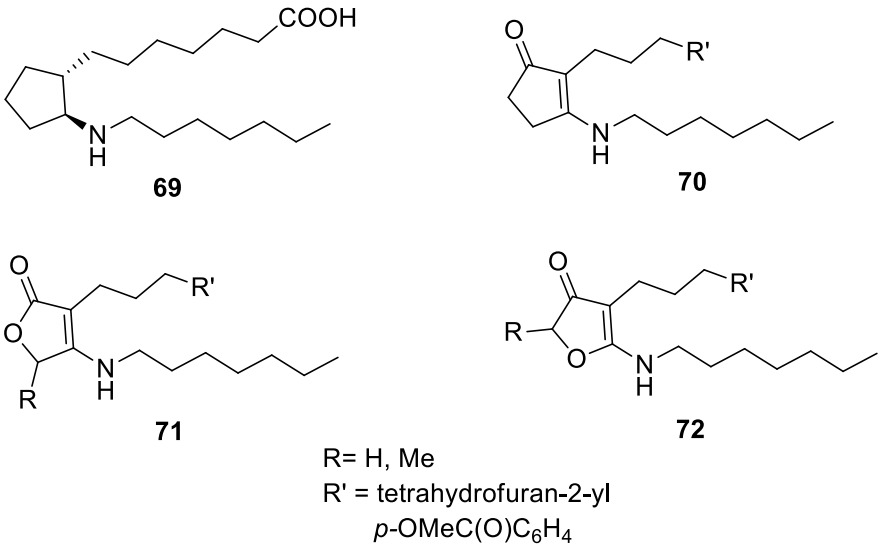


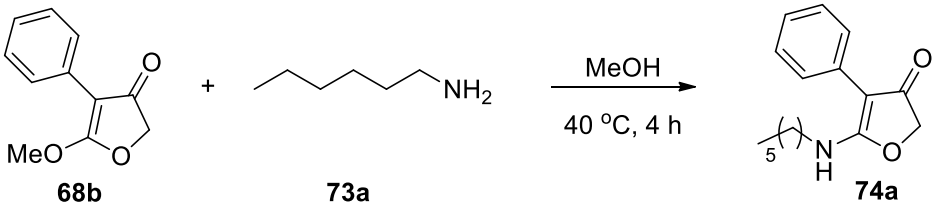
Figure 3.6. Energy profile for the mechanism of the formation of 4-aryl-3-(2*H*)-furanone.

A promising way of synthetic transformation is the replacement of one or more carbon atom with heteroatom in a skeleton. Prostaglandins (PG) are natural lipid compounds having strong physiological effects. Hence, they are widely studied as promising candidates for the development of new therapeutic agents for a number of diseases. The development of PG derived bioactive components has attracted tremendous attention of numerous chemists and pharmaceutical companies. Reports suggested that until 1984, over 5000 prostaglandin analogues have been synthesized and tested biologically. In this context, many heterocyclic analogs of prostaglandins also have been synthesized. The chemistry of prostagalndins is well established in literature, while the same with aza- analogues were limited. The pioneering work with aza-prosataglandin analogue was reported by Pashkovskii in 2004. They have synthesized 13-aza **70**, 10-oxa-13-aza **71** and 11-oxa-13-aza **72** prostanoids, structurally similar compounds of 13-azaprostanoic acid **69** with strong antiulcer properties towards ethanol-induced ulcers.[38]



Scheme 3.19

Inspired from the literature, we have synthetically modified the 3(2*H*)-furanone skeleton **68a** by introducing amine functions at the 5th position by nucleophilic substitution reaction. Our hypothesis for the synthesis of aza-prostaglandin analogues was validated by the reaction of 4-phenyl substituted furanone **68a** with *n*-hexylamine **73a** in MeOH at 40 ^{0}C. After 10 hours the reaction was complete and the aza-prostaglandin analogue **74a** was isolated in 85% yield. The structure of the product was characterized with different spectral techniques.



Scheme 3.20

In the ^{1}H NMR spectrum (Fig 3.7), aromatic protons were found to resonate in the region δ 7.42-7.20 ppm. Methylene proton (C-2) of the furanone ring showed a sharp singlet at δ 4.62 ppm. The methylene protons adjacent to the nitrogen resonated at 3.4 ppm and the aliphatic protons resonated in the region 2.04-0.88 ppm.

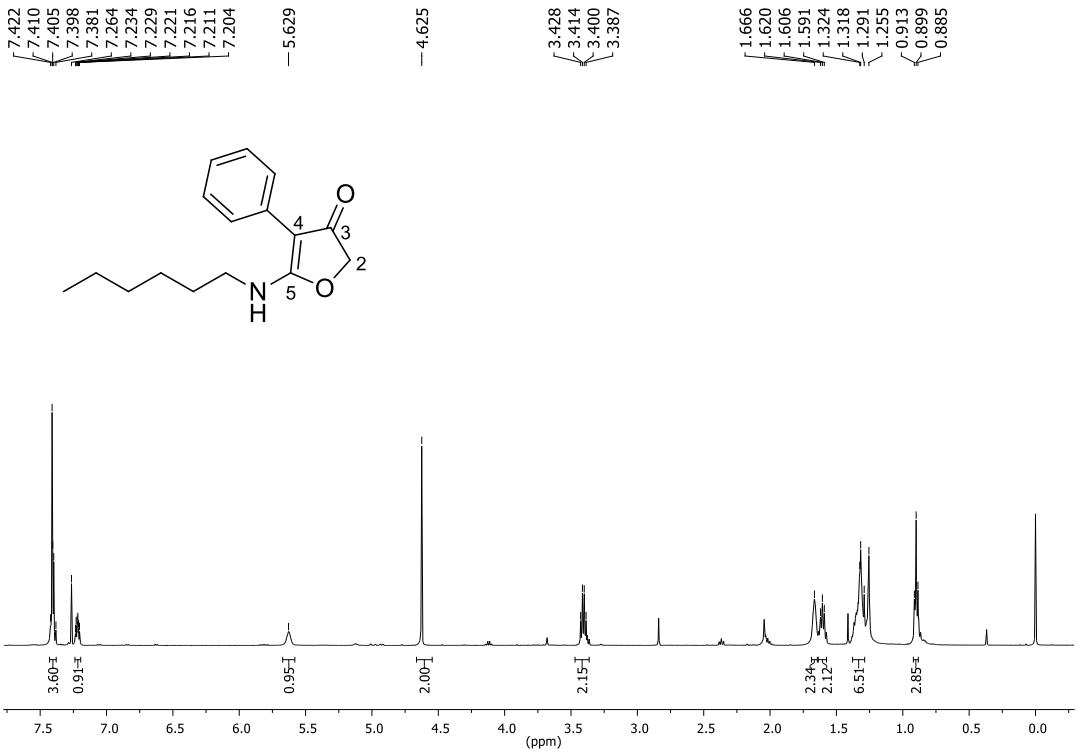


Figure 3.7. ^{1}H NMR spectrum of compound **74a**.

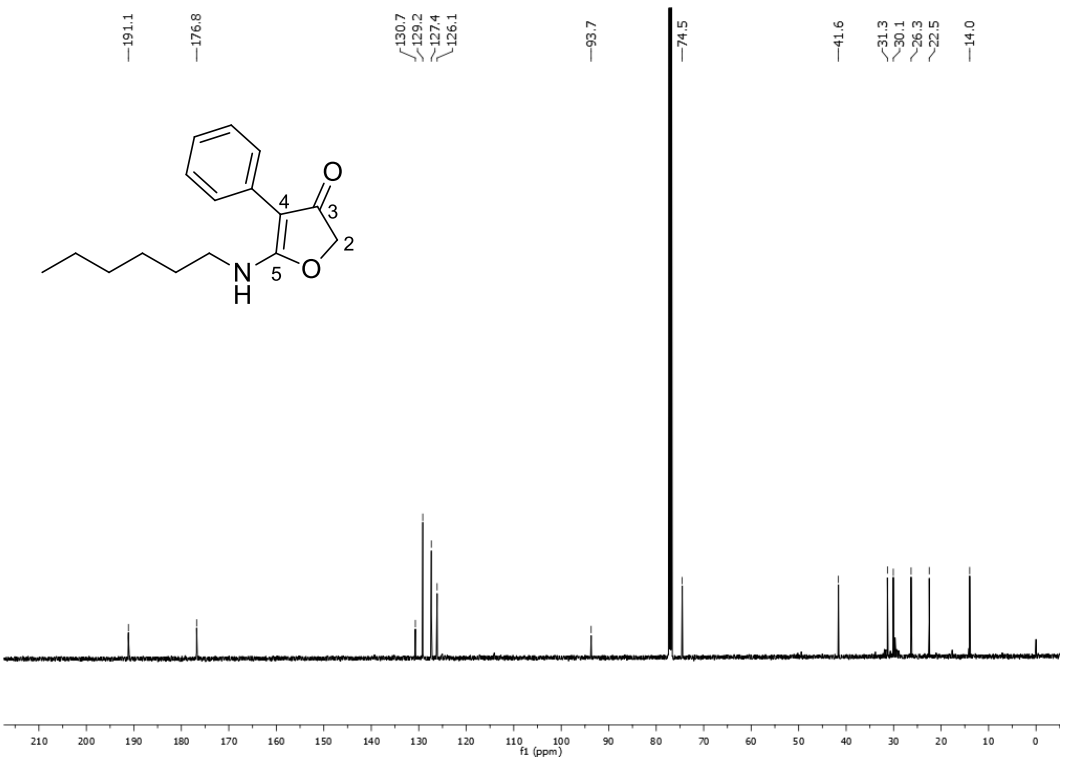


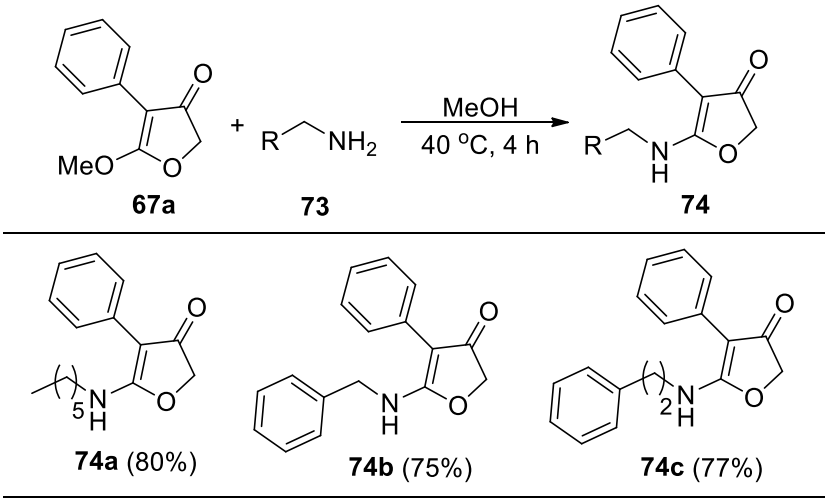
Figure 3.8. ^{13}C NMR spectrum of compound **74a**.

The ^{13}C NMR (Fig 3.8) spectra showed a peak at δ 191.5 ppm corresponding to the carbonyl carbon. Aromatic carbons resonated in the region δ 130.7-114.0 ppm. The peak at δ 93.6 ppm

is attributed to the C5 carbon and the quaternary carbon of the furanone ring attached to the NH group was found at δ 181.0 ppm. The methylene carbon of the furanone ring resonated at δ 74.5 ppm. All other peaks in the ^{1}H and ^{13}C NMR were in good agreement with the assigned structure. The assigned structure was confirmed by high resolution mass spectral analysis which showed $(M+Na)^{+}$ peak at *m/z* = 282.14295

The synthesis was further extended with benzyl amine **73b** and 2-phenylethylamine **73c**. In all the cases the corresponding azaprostaglandin analogues were isolated in good to excellent yields (Table 3.4).

Table 3.4. Synthesis of heterocyclic analogs of prostaglandins from 4-aryl-3-(2*H*)-furanone



Reaction conditions: **67a** (1.0 equiv.), **73** (1.05 equiv.), MeOH (2.0 mL), 40 °C, 4 h.

3.6 Conclusion

In conclusion, we have developed a tandem process for the synthesis of 4-aryl-3-(2*H*)-furanone from benzyne and 4-haloacetoacetates. The reaction was found to be general towards a variety of substituted arynes, and in some cases regiospecificity was observed. The reaction proceeds *via* a tandem *a*-arylation-intramolecular cyclization pathway. We have shown that additional substituents can be introduced to the 2nd or 5thposition of the 3(2*H*)-furanone moiety by using appropriately substituted 4-halo-1,3-diketo compounds. Finally, different heterocyclic analogs of prostaglandins were synthesized from 4-phenyl-3(2*H*)-furanone.

3.7 Experimental Section

3.7.1 General experimental methods: All chemicals were of the best grade commercially available and were used without further purification. Benzyne precursors 2-(trimethylsilyl)phenyl triflate, 4,5-dimethoxy-2-(trimethylsilyl)phenyl triflate, 3-methoxy-2-

(trimethylsilyl)phenyl triflate, 4-methyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate and 4-methoxy-2-(trimethylsilyl)phenyl triflate were purchased from TCI Chemicals. Benzyne precursor 2-chloro-6-(trimethylsilyl)phenyl triflate, ethyl 4-chloroacetoacetate, methyl 4-chloroacetoacetate, CsF, KF, 18-C-6 and TBAF were purchased from Sigma Aldrich. 4-Bromoacetoacetates were prepared by following reported procedures. All solvents were purified according to standard procedures; dry solvents were obtained according to the literature methods and stored over molecular sieves. Analytical thin layer chromatography was performed on polyester sheets pre-coated with silica gel containing fluorescent indicator (POLYGRAM®SIL G/UV254). Gravity column chromatography was performed using silica gel, and mixtures of hexanes/ethyl acetate were used for elution. Melting points were measured with a Büchi 530 melting point apparatus and are uncorrected. NMR spectra were recorded with Bruker Avance-300 (300 MHz for ^{1}H NMR, 75 MHz for ^{13}C{^{1}H} NMR), Bruker DRX-400 (400.1 MHz for ^{1}H NMR, 100.6 MHz for ^{13}C{^{1}H} NMR) and Bruker AMX-500 (500 MHz for ^{1}H NMR, 125 MHz for ^{13}C{^{1}H} NMR) spectrophotometer instruments. All spectra were measured at 300 K, unless otherwise specified. The chemical shifts d are given in ppm and referenced to the external standard TMS or internal solvent standard. ^{1}H NMR coupling constants (*J*) are reported in Hertz (Hz), and multiplicities are indicated as follows s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublets). Mass spectra were with a ThermoFinnigan MAT95XL, a ThermoFisher Scientific LTQ OrbitrapVelos, and an Agilent 6890 gas chromatograph with JMS-T100GC spectrometer or with a ESI/HRMS at 60,000 resolution using Thermo Scientific Exactive mass spectrometer with orbitrap analyzer.

3.7.2 Experimental procedure for synthesis of 4-aryl-3(2*H*)-furanones

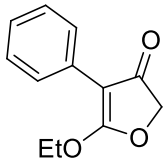
Potassium fluoride (KF) (5.0 equiv) and 18-crown-6 (5.0 equiv) were weighed into a dry Schlenk tube. The tube was degassed and purged three times with N_2. Anhydrous CH_3CN (4.0 mL) was added under N_2, after which the reaction mixture was cooled to 0 ^{o}C. Then, the benzyne precursor (1.25 equiv.) followed by 4-haloacetoacetate (1.0 equiv.) were added to the reaction mixture and stirred at 0 ^{o}C, after which the mixture was allowed to warm to RT. Upon completion of the reaction (5 h), the solvent was removed and the residue was subjected to column chromatography on silica gel (100-200 mesh), using mixtures of hexanes/ethyl acetate as eluents, affording 4-aryl-3(2*H*)-furanones.

3.7.2A. Procedure for the gram scale preparation of 4-aryl-3(2*H*)-furanone

Following the general experimental procedure, 2-(trimethylsilyl) phenyl trifluoromethanesulfonate **6** (3.72 g, 1.25 equiv.), methyl-4-chloroacetoacetate **67b** (1.5 g, 9.9 mmol), KF (2.88 g, 5.0 equiv.), 18C-6 (13.08 g, 5.0 equiv.) in CH_3CN (60 mL) at 0 ^oC and subsequent stirring at room temperature for 5 h. The crude product was purified over silica gel (100-200 mesh) column chromatography (30% ethyl acetate in hexanes) to afford the desired product **68b** as an off-white solid (1.29 g, 69%).

Synthesis and characterization of 4-aryl-3(2*H*)-furanones

5-Ethoxy-4-phenylfuran-3(2*H*)-one (68a): Following the general experimental procedure, 2-(trimethylsilyl) phenyl trifluoromethanesulfonate **6** (227 mg, 1.25 equiv.), ethyl-4-chloroacetoacetate **67a** (100 mg, 0.61 mmol), KF (177 mg, 5.0 equiv.), 18C-6 (806 mg, 5.0 equiv.) in CH_3CN (4.0 mL) at 0 ^oC and subsequent stirring at room temperature for 5 h. The crude product was purified over silica gel (100-200 mesh) column chromatography (30% ethyl acetate in hexanes) to afford the desired product **68a** as a pale brown solid (87 mg, 70%).



Analytical data of 68a

Mp; 104-106 ^oC.

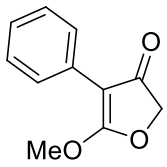
^1H NMR (300 MHz, $CDCl_3$, TMS): δ 7.80-7.77 (m, 2H), 7.31-7.26 (m, 2H), 7.15-7.10 (m, 1H), 4.61 (s, 2H), 4.52 (q, J = 9.0 Hz, 2H,), 1.45 (t, J = 9.0 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 194.1, 180.6, 129.5, 128.2, 126.0, 125.9, 93.9, 74.6, 66.6, 14.8 ppm.

HRMS (EI) m/z: $(M)^+$ calcd for $C_{12}H_{12}O_3$ 204.0786; Found: 204.0797.

5-Methoxy-4-phenylfuran-3(2*H*)-one (68b): Following the general experimental procedure, 2-(trimethylsilyl) phenyl trifluoromethanesulfonate **6** (248 mg, 1.25 equiv.), methyl-4-chloroacetoacetate **67b** (100 mg, 0.66 mmol), KF (192 mg, 5.0 equiv.), 18C-6 (872 mg, 5.0 equiv.) in CH_3CN (4.0 mL) at 0 ^oC and subsequent stirring at room temperature for 5 h. The crude product was purified over silica gel (100-200 mesh) column chromatography (30% ethyl acetate in hexanes) to afford the desired product **68b** as an off-white solid (92 mg, 73%).

Analytical data of 68b



Mp; 59-61 ^{o}C.

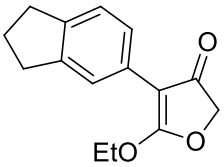
^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.78-7.75 (m, 2H), 7.31-7.26 (m, 2H), 7.15-7.10 (m, 1H), 4.62 (s, 2H), 4.12 (s, 3H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 194.1, 180.8, 129.2, 128.2, 126.1, 126.0, 94.1, 74.7, 56.7 ppm.

HRMS (EI) m/z: $(M)^+$ calcd for $C_{11}H_{10}O_3$ 190.0624; Found: 190.0628.

4-(2,3-Dihydro-1H-inden-5-yl)-5-ethoxyfuran-3(2*H*)-one (68c): Following the general experimental procedure, 6-(trimethylsilyl)indan-5-yl triflate **6b** (258 mg, 1.25 equiv.), ethyl-4-chloroacetoacetate **67a** (100 mg, 0.61 mmol), KF (177 mg, 5.0 equiv.), 18C-6 (806 mg, 5.0 equiv.) in CH_3CN (4.0 mL) at 0 ^{o}C and subsequent stirring at room temperature for 5 h. The crude product was purified over silica gel (100-200 mesh) column chromatography (30% ethyl acetate in hexanes) to afford the desired product **68c** as a pale-yellow solid (99 mg, 67%).

Analytical data of 68c



Mp; 70-72 ^{o}C.

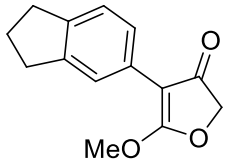
^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.63 (s, 1H), 7.51-7.47 (m, 1H), 7.16-7.13 (d, *J* = 6.0 Hz, 1H), 4.59 (s, 2H), 4.49 (q, *J* = 6.0 Hz, 2H), 2.87-2.79 (m, 4H), 2.03-1.93 (m, 2H), 1.43 (t, 3H, *J* = 6.0 Hz) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): 194.3, 180.5, 144.1, 142.1, 127.0, 124.1, 124.1, 122.2, 94.4, 74.5, 66.5, 33.0, 32.7, 25.5, 14.9. ppm.

HRMS (EI) m/z: $(M)^+$ calcd for $C_{15}H_{16}O_3$ 244.1094; Found: 244.1086.

4-(2,3-Dihydro-1H-inden-5-yl)-5-methoxyfuran-3(2*H*)-one (68d): Following the general experimental procedure, 6-(trimethylsilyl)indan-5-yl triflate **6b** (279 mg, 1.25 equiv.), methyl-4-chloroacetoacetate **67b** (100 mg, 0.66 mmol), KF (192 mg, 5.0 equiv.), 18C-6 (872 mg, 5.0 equiv.) in CH_3CN (4.0 mL) at 0 ^{o}C and subsequent stirring at room temperature for 5 h. The crude product was purified over silica gel (100-200 mesh) column chromatography (30% ethyl acetate in hexanes) to afford the desired product **68d** as a pale-yellow solid (103 mg, 68%).

Analytical data of 68d



Mp; 123-125 ^{o}C.

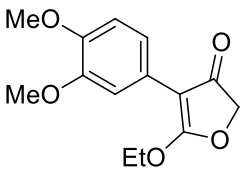
^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.60 (s, 1H), 7.50-7.47 (m, 1H), 7.15-7.13 (d, *J* = 6.0 Hz, 1H), 4.61 (s, 2H), 4.10 (s, 3H), 2.87-2.79 (m, 4H), 2.03-1.94 (m, 2H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 194.3, 180.7, 144.2, 142.2, 126.7, 124.2, 124.1, 122.3, 94.6, 74.6, 56.5, 33.0, 32.7, 25.5 ppm.

HRMS (EI) m/z: $(M)^+$ calcd for $C_{14}H_{14}O_3$ 230.0937; Found: 230.0933.

4-(3,4-Dimethoxyphenyl)-5-ethoxyfuran-3(2*H*)-one (68e): Following the general experimental procedure, 4,5-dimethoxy-2-(trimethylsilyl)phenyl triflate **6c** (273 mg, 1.25 equiv.), ethyl-4-chloroacetoacetate **67a** (100 mg, 0.61 mmol), KF (177 mg, 5.0 equiv.), 18C-6 (806 mg, 5.0 equiv.) in CH_3CN (4.0 mL) at 0 ^{o}C and subsequent stirring at room temperature for 5 h. The crude product was purified over silica gel (100-200 mesh) column chromatography (30% ethyl acetate in hexanes) to afford the desired product **68e** as a pale brown solid (103 mg, 67%).

Analytical data of 68e



Mp; 136-138 ^{o}C.

^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.51 (d, *J* = 1.8 Hz, 1H,), 7.32 (dd, , J_1 = 8.4 Hz, J_2= 2.1 Hz, 1H), 6.80 (d, *J* = 8.4 Hz, 1H), 4.59 (s, 2H), 4.51 (q, *J* =7.2 Hz, 2H,), 3.84 (s, 3H), 3.81 (s, 3H), 1.45 (t, *J* = 7.2 Hz, 3H,) ppm.

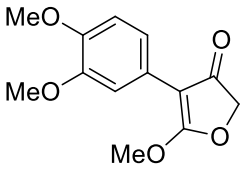
^{13}C NMR (75 MHz, $CDCl_3$): 194.2, 180.2, 148.6, 147.1, 122.3, 118.4, 111.0, 109.5, 74.5, 66.5, 55.8, 55.7, 14.8 ppm.

HRMS (EI) m/z: $(M)^+$ calcd for $C_{14}H_{16}O_5$ 264.0992; Found: 264.0984.

4-(3,4-Dimethoxyphenyl)-5-methoxyfuran-3(2*H*)-one (68f): Following the general experimental procedure, 4,5-dimethoxy-2-(trimethylsilyl)phenyl triflate **6c** (296 mg, 1.25 equiv.), methyl-4-chloroacetoacetate **67b** (100 mg, 0.66 mmol), KF (192 mg, 5.0 equiv.), 18C-6 (872 mg, 5.0 equiv.) in CH_3CN (4.0 mL) at 0 ^{o}C and subsequent stirring at room temperature

for 5 h. The crude product was purified over silica gel (100-200 mesh) column chromatography (30% ethyl acetate in hexanes) to afford the desired product **68f** as a brown solid (110 mg, 68%).

Analytical data of 68f



Mp; 122-124 ^{o}C.

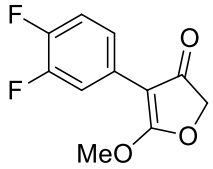
^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.47 (d, *J* = 2.1 Hz, 1H), 7.27 (dd, J_1 = 8.4 Hz, J_2= 2.1 Hz, 1H), 6.78 (d, *J* = 8.4 Hz, 1H,), 4.61 (s, 2H), 4.12 (s, 3H), 3.84 (s, 3H), 3.81 (s, 3H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 194.2, 180.5, 148.6, 147.3, 122.1, 118.5, 111.1, 109.7, 74.6, 56.7, 55.9 ppm.

HRMS (EI) m/z: $(M)^+$ calcd for $C_{13}H_{14}O_5$ 250.0836; Found: 250.0828.

4-(3,4-Difluorophenyl)-5-methoxyfuran-3(2*H*)-one (68g): Following the general experimental procedure, 4,5-difluoro-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **6d** (276 mg, 1.25 equiv.), methyl-4-chloroacetoacetate **67b** (100 mg, 0.66 mmol), KF (192 mg, 5.0 equiv.), 18C-6 (872 mg, 5.0 equiv.) in CH_3CN (4.0 mL) at 0 ^{o}C for 2 h. The crude product was purified over silica gel (100-200 mesh) column chromatography (30% ethyl acetate in hexanes) to afford the desired product **68g** as a light-yellow oil (72 mg, 48%).

Analytical data of 68g



TLC (SiO_2): R_f; 0.26 (50% ethyl acetate in hexane).

^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.72-7.65 (m, 1H), 7.60-7.55 (m, 1H), 7.09-7.00 (m, 1H), 4.63 (s, 2H), 4.15 (s, 3H) ppm.

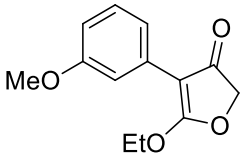
^{13}C NMR (75 MHz, $CDCl_3$): δ 193.6, 180.6, 121.8 (d, *J* = 12.5 Hz, 7Hz), 116.9 (d, *J* = 29.0 Hz), 114.6 (d, *J* = 25.0 H), 92.5, 74.8, 57.0 ppm.

HRMS (EI) m/z: $(M)^+$ calcd for $C_{11}H_8F_2O_3$ 226.0436; Found: 226.0441.

5-Ethoxy-4-(3-methoxyphenyl)furan-3(2*H*)-one (68h): Following the general experimental procedure, 3-methoxy-2-(trimethylsilyl)phenyl triflate **6e** (250 mg, 1.25 equiv.), ethyl-4-

chloroacetoacetate **67a** (100 mg, 0.61 mmol), KF (177 mg, 5.0 equiv.), 18C-6 (806 mg, 5.0 equiv.) in CH_3CN (4.0 mL) at 0 ^oC and subsequent stirring at room temperature for 5 h. The crude product was purified over silica gel (100-200 mesh) column chromatography (30% ethyl acetate in hexanes) to afford the desired product **68h** as a pale yellow solid (101 mg, 71%).

Analytical data of 68h



Mp; 67-69 ^oC.

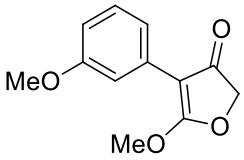
^1H NMR (300 MHz, $CDCl_3$, TMS): δ 7.45-7.44 (m, 1H), 7.42-7.38 (m, 1H), 7.22-7.17 (m, 1H), 6.71-6.66 (m, 1H), 4.60 (s, 2H), 4.52 (q, *J* = 6.0 Hz, 2H,), 3.75 (s, 3H), 1.45 (t, *J* = 6.0 Hz, 3H,) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): 194.1, 180.6, 159.4, 130.8, 129.1, 118.4, 111.8, 111.3, 93.7, 74.6, 66.7, 55.2, 14.8. ppm.

HRMS (EI) m/z: $(M)^+$ calcd for $C_{13}H_{14}O_4$ 234.0886; Found: 264.0882.

5-Methoxy-4-(3-methoxyphenyl)furan-3(2*H*)-one (68i): Following the general experimental procedure, 3-methoxy-2-(trimethylsilyl)phenyl triflate **6e** (271 mg, 1.25 equiv.), methyl-4-chloroacetoacetate **67b** (100 mg, 0.66 mmol), KF (192 mg, 5.0 equiv.), 18C-6 (872 mg, 5.0 equiv.) in CH_3CN (4.0 mL) at 0 ^oC and subsequent stirring at room temperature for 5 h. The crude product was purified over silica gel (100-200 mesh) column chromatography (30% ethyl acetate in hexanes) to afford the desired product **68i** as a pale-yellow solid (106 mg, 73%).

Analytical data of 68i



Mp; 95-97 ^oC.

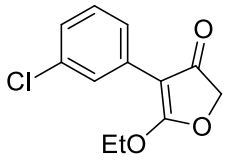
^1H NMR (300 MHz, $CDCl_3$, TMS): δ 7.42-7.41 (m, 1H), 7.39-7.35 (m, 1H), 7.22-7.17 (m, 1H), 6.71-6.67 (m, 1H), 4.61 (s, 2H), 4.12 (s, 3H), 3.75 (s, 3H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 194.0, 180.8, 159.4, 130.6, 129.1, 118.5, 111.7, 111.5, 93.9, 74.7, 56.7, 55.2 ppm.

HRMS (EI) m/z: $(M)^+$ calcd for $C_{12}H_{12}O_4$ 220.0730; Found: 220.0725.

4-(3-Chlorophenyl)-5-ethoxyfuran-3(2*H*)-one (68j): Following the general experimental procedure, 2-chloro-6-(trimethylsilyl)phenyl triflate **6f** (253 mg, 1.25 equiv.), ethyl-4-chloroacetoacetate **67a** (100 mg, 0.61 mmol), KF (177 mg, 5.0 equiv.), 18C-6 (806 mg, 5.0 equiv.) in CH_3CN (4.0 mL) at 0 ^oC for 4 h. The crude product was purified over silica gel (100-200 mesh) column chromatography (30% ethyl acetate in hexanes) to afford the desired product **68j** as a pale-yellow viscous liquid (89 mg, 61%).

Analytical data of 68j



TLC (SiO_2): R_f; 0.37 (50% ethyl acetate in hexane).

^1H NMR (500 MHz, $CDCl_3$, TMS): δ 7.89 (t, , J = 1.5 Hz, 1H), 7.81 (d, J = 8Hz, 1H), 7.28 (d, J = 8 Hz, 1H ,), 7.16 (dd, J_1 = 7.5 Hz, J_2 = 1.0 Hz, 1H) 4.69 (s, 2H) 4.62 (q, J = 6.0 Hz, 2H) 1.54 (t, J = 6.0 Hz, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): 193.7, 180.6, 134.1, 129.4, 125.9, 125.6, 123.8, 74.7, 67.0, 14.9 ppm.

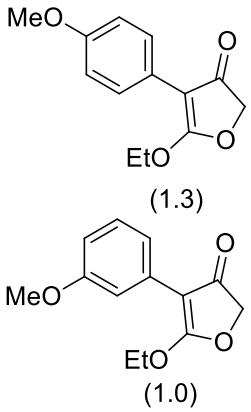
HRMS (ESI): calcd for $C_{12}H_{11}ClNaO_3$, $(M+Na)^+$: 261.0289, Found: 261.0298.

5-Ethoxy-4-(4-methoxyphenyl)furan-3(2*H*)-one & 5-ethoxy-4-(3-methoxyphenyl)furan-3(2*H*)-one (68k): Following the general experimental procedure, 4-methoxy-2-(trimethylsilyl)phenyl triflate **6g** (250 mg, 1.25 equiv.), ethyl-4-chloroacetoacetate **67a** (100 mg, 0.61 mmol), KF (177 mg, 5.0 equiv.), 18C-6 (806 mg, 5.0 equiv.) in CH_3CN (4.0 mL) at 0 ^oC and subsequent stirring at room temperature for 5 h. The crude product was purified over silica gel (100-200 mesh) column chromatography (30% ethyl acetate in hexanes) to afford the desired product **68k** as a pale yellow solid and as regioisomers in a ratio of 1:1.3 (96 mg, 67%).

Analytical data of 68k

Mp; 132-134 ^oC.

^1H NMR (300 MHz, $CDCl_3$, TMS): δ 7.74-7.69 (m, 2.6H), 7.45-7.44 (m, 1H), 7.41-7.38 (m, 1H), 7.22-7.17 (m, 1H), 6.86-6.81 (m, 2.6H), 6.70-6.66 (m, 1H), 4.59 (s, 2H), 4.58 (s, 2.6H), 4.55-4.46 (m, 4.6H), 3.75 (s, 3H), 3.73 (s, 3.9H) 1.47-1.41 (m, 7H) ppm.

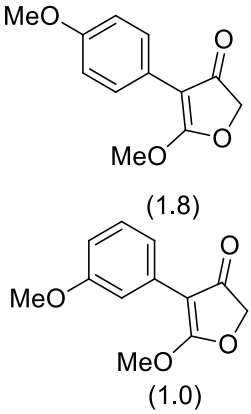


^{13}C NMR (75 MHz, $CDCl_3$): 194.2, 194.0, 180.6, 180.2, 159.4, 157.7, 130.8, 129.1, 127.2, 121.9, 118.4, 113.7, 111.7, 111.3, 93.7, 93.6, 74.5, 74.5, 66.7, 66.5, 55.2, 55.1, 14.9, 14.8 ppm.

HRMS (EI) m/z: $(M)^+$ calcd for $C_{13}H_{14}O_4$ 234.0887; Found: 264.0888.

5-Methoxy-4-(4-methoxyphenyl)furan-3(2*H*)-one & 5-methoxy-4-(3-methoxyphenyl)furan-3(2*H*)-one (68l): Following the general experimental procedure, 4-methoxy-2-(trimethylsilyl)phenyl triflate **6g** (271 mg, 1.25 equiv.), methyl-4-chloroacetoacetate **67b** (100 mg, 0.66 mmol), KF (192 mg, 5.0 equiv.), 18C-6 (872 mg, 5.0 equiv.) in CH_3CN (4.0 mL) at 0 ^oC and subsequent stirring at room temperature for 5 h. The crude product was purified over silica gel (100-200 mesh) column chromatography (30% ethyl acetate in hexanes) to afford the desired product **68l** as a pale yellow and as regioisomers in a ratio of 1:1.8 (102 mg, 70%).

Analytical data of 68l



Mp; 86-88 ^oC.

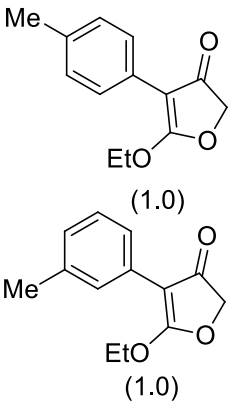
^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.71-7.66 (m, 3.7H), 7.42-7.41 (m, 1H), 7.39-7.35 (m, 1H), 7.22-7.17 (m, 1H), 6.86-6.81 (m, 3.8H), 6.71-6.67 (m, 1H), 4.61 (s, 2H), 4.60 (s, 3.6H), 4.12 (s, 3H), 4.10 (s, 5.7H), 3.75 (s, 3H), 3.73 (s, 5.6H).

^{13}C NMR (75 MHz, $CDCl_3$): 194.2, 180.5, 159.5, 157.8, 130.6, 129.1, 127.3, 121.7, 118.5, 113.7, 111.7, 111.5, 93.9, 74.7, 56.6, 55.2 ppm.

HRMS (EI) m/z: $(M)^+$ calcd for $C_{12}H_{12}O_4$ 220.0730; Found: 264.0726.

5-Ethoxy-4-(p-tolyl)furan-3(2*H*)-one & 5-ethoxy-4-(m-tolyl)furan-3(2*H*)-one (68m): Following the general experimental procedure, 4-methyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **6h** (238 mg, 1.25 equiv.), ethyl-4-chloroacetoacetate **67a** (100 mg, 0.61 mmol), KF (177 mg, 5.0 equiv.), 18C-6 (806 mg, 5.0 equiv.) in CH_3CN (4.0 mL) at 0 ^oC

and subsequent stirring at room temperature for 5 h. The crude product was purified over silica gel (100-200 mesh) column chromatography (30% ethyl acetate in hexanes) to afford the desired product **68m** as a pale brown solid and as regioisomers in a ratio of 1:1 (95 mg, 71%).



Analytical data of 68m

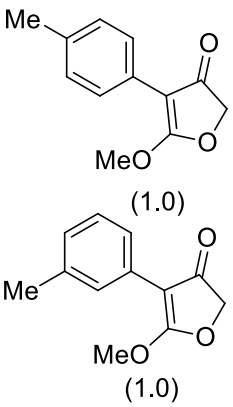
Mp; 75-77 ^{o}C.

^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.69-7.64 (m, 2H), 7.63-7.62 (m, 1H), 7.55-7.52 (m, 1H), 7.20-7.15 (m, 1H), 7.11-7.07 (m, 2H), 6.96-6.93 (m, 1H), 4.59 (s, 2H), 4.59 (s, 2H), 4.54-4.46 (m, 4H), 2.29 (s, 3H), 2.26 (s, 3H) 1.46-1.41 (m, 6H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): 194.2, 194.2, 180.6, 180.5, 137.7, 135.5 129.2, 128.9, 128.1, 126.8, 126.7, 126.4, 125.9, 123.1, 94.0, 93.9, 74.5, 66.6, 66.5, 21.6, 21.2, 14.8 ppm.

HRMS (EI) m/z: $(M)^{+}$ calcd for $C_{13}H_{14}O_3$ 218.0937; Found: 218.0926.

5-Methoxy-4-(p-tolyl)furan-3(2*H*)-one & 5-methoxy-4-(m-tolyl)furan-3(2*H*)-one (68n): Following the general experimental procedure, 4-methyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **6h** (258 mg, 1.25 equiv.), methyl-4-chloroacetoacetate **67b** (100 mg, 0.66 mmol), KF (192 mg, 5.0 equiv.), 18C-6 (872 mg, 5.0 equiv.) in CH_3CN (4.0 mL) at 0 ^{o}C and subsequent stirring at room temperature for 5 h. The crude product was purified over silica gel (100-200 mesh) column chromatography (30% ethyl acetate in hexanes) to afford the desired product **68n** as a pale brown solid and as regioisomers in a ratio of 1:1 (101 mg, 75%).



Analytical data of 68n

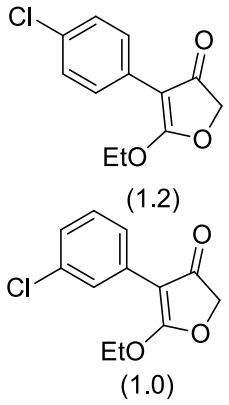
Mp; 57-59 ^{o}C.

^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.66-7.62 (m, 2H), 7.59-7.58 (m, 1H), 7.54-7.51 (m, 1H), 7.20-7.14 (m, 1H), 7.11-7.08 (m, 2H), 6.96-6.93 (m, 1H), 4.61 (s, 2H), 4.60 (s, 2H), 4.10 (s, 3H), 4.10 (s, 3H), 2.29 (s, 3H), 2.26 (s, 3H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): 194.2, 194.2, 180.8, 180.7, 137.7, 135.7, 129.0, 128.9, 128.1, 126.9, 126.7, 126.2, 125.9, 123.2, 94.2, 94.0, 74.7, 56.6, 56.6, 21.6, 21.2 ppm.

HRMS (EI) m/z: $(M)^+$ calcd for $C_{12}H_{12}O_3$ 204.0786; Found: 204.0796.

4-(4-Chlorophenyl)-5-ethoxyfuran-3(2*H*)-one & 4-(3-chlorophenyl)-5-ethoxyfuran-3(2*H*)-one (68o): Following the general experimental procedure, 4-chloro-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **6i** (254 mg, 1.25 equiv.), ethyl-4-chloroacetoacetate **67a** (100 mg, 0.61 mmol), KF (177 mg, 5.0 equiv.), 18C-6 (806 mg, 5.0 equiv.) in CH_3CN (4.0 mL) at 0 ^oC for 4 h. The crude product was purified over silica gel (100-200 mesh) column chromatography (30% ethyl acetate in hexanes) to afford the desired product **68o** as a pale-yellow oil and as regioisomers in a ratio of 1:1.2 (90 mg, 62%).



Analytical data of 68o

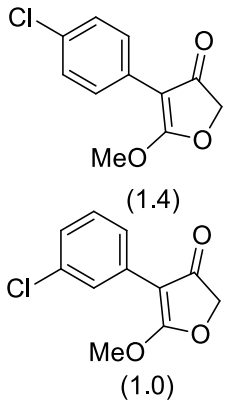
TLC (SiO_2): R_f; 0.38 (50% ethyl acetate in hexane).

^1H NMR (300 MHz, $CDCl_3$, TMS): δ 7.82-7.81 (m, 1H), 7.79-7.72 (m, 3.6H), 7.26-7.19 (m, 3.4H), 7.10-7.06 (m, 1H), 4.61 (s, 2H), 4.61 (s, 2.4H), 4.58-4.40 (m, 4.4H), 1.49-1.43 (m, 6.6H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): 194.0, 193.8, 180.6, 180.5, 134.0, 131.3, 131.3, 129.4, 128.3, 128.0, 127.0, 125.9, 125.6, 123.7, 93.0, 92.8, 74.7, 67.1, 67.0, 14.8 ppm.

HRMS (EI) m/z: $(M)^+$ calcd for $C_{12}H_{11}ClO_3$ 238.0397; Found: 218.0408.

4-(4-Chlorophenyl)-5-methoxyfuran-3(2*H*)-one & 4-(3-chlorophenyl)-5-methoxyfuran-3(2*H*)-one (68p): Following the general experimental procedure, 4-chloro-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **6i** (275 mg, 1.25 equiv.), methyl-4-chloroacetoacetate **67b** (100 mg, 0.66 mmol), KF (192 mg, 5.0 equiv.), 18C-6 (872 mg, 5.0 equiv.) in CH_3CN (4.0 mL) at 0 ^oC for 4 h. The crude product was purified over silica gel (100-200 mesh) column chromatography (30% ethyl acetate in hexanes) to afford the desired product **68p** as a pale-yellow oil and as regioisomers in a ratio of 1:1.4 (101 mg, 66%).



Analytical data of 68p

TLC (SiO_2): R_f; 0.32 (50% ethyl acetate in hexane).

^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.79-7.77 (m, 1H), 7.76-7.71 (m, 3.8H), 7.25-7.17 (m, 3.8H), 7.10-7.07 (m, 1H), 4.62 (s, 2H), 4.62 (s, 2.8H), 4.14 (s, 3H), 4.13 (s, 4.2H) ppm.

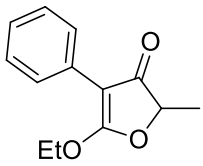
^{13}C NMR (75 MHz, $CDCl_3$): 193.9, 193.7, 180.9, 180.8, 134.1, 131.4, 131.1, 129.4, 128.3, 127.8, 127.1, 126.0, 125.6, 123.8, 93.2, 93.0, 74.8, 56.9, 56.9 ppm.

HRMS (EI) m/z: $(M)^+$ calcd for $C_{11}H_9ClO_3$ 224.0240; Found: 2224.0252.

5-ethoxy-2-methyl-4-phenylfuran-3(2*H*)-one (68q): Following the general experimental procedure, 2-(trimethylsilyl) phenyl trifluoromethanesulfonate **6** (167 mg, 1.25 equiv.), ethyl 4-bromo-3-oxopentanoate **67c** (100 mg, 0.45 mmol), KF (130 mg, 5.0 equiv.), 18C-6 (592 mg, 5.0 equiv.) in CH_3CN (3.0 mL) at 0 °C and subsequent stirring at room temperature for 5 h. The crude product was purified over silica gel (100-200 mesh) column chromatography (30% ethyl acetate in hexanes) to afford the desired product **68q** as a pale-yellow solid (69 mg, 69%).

Analytical data of 68q

Mp; 77-79 °C.



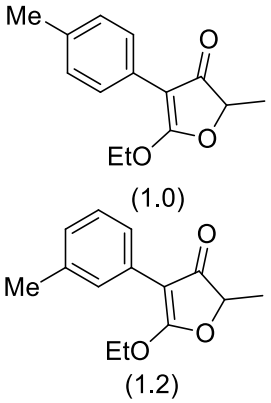
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.88 (d, *J* = 7.5 Hz, 2H), 7.35 (t, *J* = 7.5 Hz, 2H), 7.18 (t, *J* = 7.0 Hz, 1H), 4.74 (q, *J* = 7.0 Hz, 1H ,), 4.58 (q, *J* = 7.0 Hz, 2H ,), 1.57 (d, *J* = 7.0 Hz, 3H), 1.52 (t, *J* = 7.0 Hz, 3H ,) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 196.9, 179.2, 129.8, 128.2, 125.9, 125.8, 92.4, 82.8, 66.4, 16.7, 14.8 ppm.

HRMS (ESI) m/z: calcd for $C_{13}H_{14}NaO_3$, $(M+Na)^+$: 241.0835, Found: 241.0826.

5-Ethoxy-2-methyl-4-(p-tolyl)furan-3(2*H*)-one & 5-ethoxy-2-methyl-4-(m-tolyl)furan-3(2*H*)-one (68r): Following the general experimental procedure, 4-methyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **6h** (176 mg, 1.25 equiv.), ethyl 4-bromo-3-oxopentanoate **67c** (100 mg, 0.45 mmol), KF (130 mg, 5.0 equiv.), 18C-6 (592 mg, 5.0 equiv.)

in CH_3CN (3.0 mL) at 0 °C and subsequent stirring at room temperature for 5 h. The crude product was purified over silica gel (100-200 mesh) column chromatography (30% ethyl acetate in hexanes) to afford the desired product **68r** as a pale yellow solid and as regioisomers in a ratio of 1.2:1 (66 mg, 63%).



Analytical data of 68r

Mp; 140-142 °C.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.76-7.73 (m, 3.2H), 7.62 (d, *J* = 8.0 Hz ,1.2H) 7.24 (t, *J* = 8.0 Hz, 1.2H), 7.16 (d, *J* = 8.5 Hz, 2H), 7.00 (d, *J* = 7.5 Hz, 1.2H ,) 4.75-4.70 (m, 2.2H), 4.60-4.55 (m, 4.4H), 2.36 (s, 3.6H), 2.33 (s, 3H), 1.57 (d, *J* = 1.5 Hz, 3.6H), 1.56 (d, *J*= 1.5Hz, 3H), 1.53-1.49 (m, 6.6H) ppm.

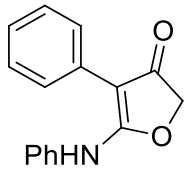
^{13}C NMR (125 MHz, $CDCl_3$): 197.0, 179.3, 179.1, 137.7, 135.4, 129.6, 128.9, 128.1, 126.8, 126.7, 126.7, 125.9, 123.1, 92.5, 92.4, 82.8, 66.4, 66.3, 21.6, 21.2, 16.7, 14.9. ppm.

HRMS (ESI) m/z: calcd for $C_{14}H_{16}NaO_3$, $(M+Na)^+$: 255.0992, Found: 255.0984.

4-phenyl-5-(phenylamino)furan-3(2H)-one (68u). Following the general experimental procedure, 2-(trimethylsilyl) phenyl trifluoromethanesulfonate **6** (148 mg, 1.25 equiv.), 4-bromo-3-oxo-*N*-phenylbutanamide **67e** (100 mg, 0.39 mmol), KF (114 mg, 5.0 equiv.), 18C-6 (516 mg, 5.0 equiv.) in CH_3CN (3.0 mL) at 0 °C and subsequent stirring at room temperature for 5 h. The crude product was purified over silica gel (100-200 mesh) column chromatography (40% ethyl acetate in hexanes) to afford the desired product **68u** as a pale brown solid (51 mg, 52%).

Analytical data of 68u

Mp: 158-160 °C.



^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.43-7.38 (m, 3H), 7.37-7.36 (m, 1H), 7.35-7.32 (m, 1H), 7.30-7.29 (m, 1H), 7.28-7.26 (m, 1H),7.24-7.20 (m, 3H), 7.15-7.09 (m, 1H), 4.65 (s, 2H) ppm.

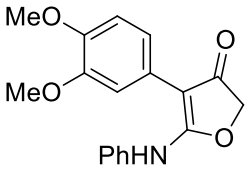
$^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$): 192.2, 174.9, 136.2, 130.2, 129.8, 129.8, 128.3, 127.3, 125.8, 121.8, 96.4, 75.2 ppm.

HRMS (EI) m/z: calcd for $C_{16}H_{13}NO_2$, $(M)^+$: 251.0946, Found: 251.0941.

4-(3,4-dimethoxyphenyl)-5-(phenylamino)furan-3(2H)-one (68v). Following the general experimental procedure, 4,5-dimethoxy-2-(trimethylsilyl)phenyl triflate **6c** (175 mg, 1.25 equiv.), 4-bromo-3-oxo-*N*-phenylbutanamide **67e** (100 mg, 0.39 mmol), KF (114 mg, 5.0 equiv.), 18C-6 (516 mg, 5.0 equiv.) in CH_3CN (3.0 mL) at 0 °C and subsequent stirring at room temperature for 5 h. The crude product was purified over silica gel (100-200 mesh) column chromatography (80% ethyl acetate in hexanes) to afford the desired product **68v** as an amorphous solid (58 mg, 48%).

Analytical data of 68v

TLC (SiO_2): R_f 0.29 (80% ethyl acetate in hexane).



^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.33-7.28 (m, 3H), 7.24-7.21 (m, 2H), 7.15-7.09 (m, 1H), 6.99 (s, 1H), 6.86 (s, 2H), 4.69 (s, 2H), 3.82 (s, 6H) ppm.

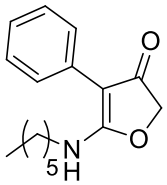
$^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$): 191.7. 174.5, 149.7, 148.1, 135.9, 129.4, 125.3, 122.2, 121.1, 119.9, 111.9, 111.9, 96.0, 74.9, 56.0 ppm.

HRMS (EI) m/z: calcd for $C_{18}H_{17}NO_4$, $(M)^+$: 311.1158, Found: 311.1152.

5-(hexylamino)-4-phenylfuran-3(2H)-one (74a): 5-methoxy-4-phenylfuran-3(2*H*)-one **68a** (100 mg, 1.0 equiv., 0.53 mmol) and *n*-hexylamine **73a** (1.1 equiv.) were weighed into a dry Schlenk tube. Dry methanol (2.0 mL) was added and the reaction mixture was stirred at 40 °C for 4 h. Upon completion of the reaction, the solvent was removed and the residue was subjected to column chromatography on neutral alumina using hexanes/ethyl acetate mixture as eluent to afford the product **74a** as a pale-yellow viscous liquid (110 mg, 80%).

Analytical data of 74a

TLC (SiO_2): R_f; 0.23 (50% ethyl acetate in hexane).



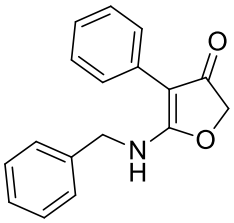
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.42-7.38 (m, 4H), 7.22-7.20 (m, 1H), 5.63 (brs, 1H), 4.62 (s, 2H), 3.41 (m, 2H), 1.67-1.66 (m, 2H), 1.62-1.59 (m, 2H), 1.32-1.25 (m, 4H), 0.90 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 191.1, 176.8, 130.7, 129.2, 127.4, 126.1, 93.7, 74.5, 41.6, 31.3, 30.1, 29.7, 26.3, 22.5, 13.9 ppm.

HRMS (ESI) m/z: $(M+Na)^+$ calcd for $C_{16}H_{21}NNaO_2$ 282.1465; Found: 282.1455.

5-(benzylamino)-4-phenylfuran-3(2*H*)-one (74b): 5-methoxy-4-phenylfuran-3(2*H*)-one **68a** (100 mg, 1.0 equiv., 0.53 mmol) and benzylamine **73b** (1.1 equiv.) were weighed into a dry Schlenk tube. Dry methanol (2.0 mL) was added and the reaction mixture was stirred at 40 ^{o}C for 4 h. Upon completion of the reaction, the solvent was removed and the residue was subjected to column chromatography on neutral alumina using hexanes/ethyl acetate mixture as eluent to afford the product **74b** as a pale-yellow viscous liquid (105 mg, 75%).

Analytical data of 74b



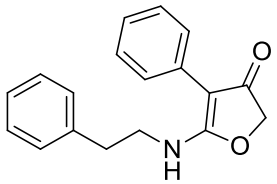
TLC (SiO_2): R_f; 0.19 (50% ethyl acetate in hexane).

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ **7.**42- 7.29 (m, 9H), 7.21-7.19 (m, 1H), 5.9 (brs, 1H), 4.65 (s, 2H), 4.60 (d, *J* = 6.0 Hz, 2H,) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 191.5, 176.5, 136.8, 130.4, 129.1, 129.1, 128.2, 127.5, 127.4, 126.3, 94.1, 74.6, 45.4 ppm.

HRMS (ESI) m/z: $(M+Na)^+$ calcd for $C_{17}H_{15}NNaO_2$ 288.0995; Found: 288.0988.

5-(phenethylamino)-4-phenylfuran-3(2*H*)-one (74c): 5-methoxy-4-phenylfuran-3(2*H*)-one **68a** (100 mg, 1.0 equiv., 0.53 mmol) and 2-phenylethylamine **73c** (1.1 equiv.) were weighed into a dry Schlenk tube. Dry methanol (2.0 mL) was added and the reaction mixture was stirred at 40 ^{o}C for 4 h. Upon completion of the reaction, the solvent was removed and the residue was subjected to column chromatography on neutral alumina using hexanes/ethyl acetate mixture as eluent to afford the product **25** as a pale-yellow viscous liquid (114 mg, 77%).



Analytical data of 74c

TLC (SiO_2): R_f; 0.18 (50% ethyl acetate in hexane).

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.36- 7.19 (m, 10H), 5.58 (brs, 1H), 4.62 (s, 2H), 3.68 (q, *J* = 6.3 Hz, 2H ,), 2.92 (t, *J* = 6.6 Hz, 2H ,) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 190.4, 176.7, 137.5, 132.2, 132.1, 129.1, 129.0, 128.8, 128.6, 127.4, 127.2, 126.5, 94.5, 74.8, 42.8, 36.2 ppm.

HRMS (ESI) m/z: $(M+Na)^+$ calcd for $C_{18}H_{17}NNaO_2$ 302.1152; Found: 302.1157.

3.7.3 DFT Calculations

The geometry optimizations were done at M06L/SMD/6-311G(d,p) level density functional theory.[39-41] M06L stands for the Minnesota 2006 local exchange−correlation functional[40] while SMD describes the self-consistent reaction field method to simulate the implicit solvation effect.[40] The selected solvent is acetonitrile. M06L functional is regarded as one of the most accurate local functionals currently available for describing energy barriers and non-covalent interactions.[39, 41] All the transition states were characterized by a single imaginary frequency along the reaction coordinate, whereas all the intermediates were confirmed to be a minimum by locating zero imaginary frequency in the vibrational frequency analysis. All the calculations were done with the *Gaussian 16* suite of programmes.[42]

Coordinates of Optimized Geometries in Å followed by energy parameters in au.

a

C	-1.593890000	-0.127224000	0.101975000
C	-0.581852000	0.137841000	-0.962809000
H	-0.376662000	1.247359000	-0.912828000
C	0.771946000	-0.485861000	-0.721238000
C	1.489898000	0.173143000	0.418541000
H	0.944648000	-0.002661000	1.347886000
H	1.446337000	1.263860000	0.214119000
O	1.245190000	-1.336250000	-1.443298000
O	-1.383679000	-0.213910000	1.292974000

O	-2.826582000	-0.223197000	-0.431265000
C	-3.885937000	-0.407522000	0.518457000
H	-3.745730000	-1.332313000	1.081382000
H	-3.933736000	0.432335000	1.214372000
H	-4.801562000	-0.461030000	-0.066552000
Cl	3.176598000	-0.393199000	0.636547000
H	-0.960776000	-0.160495000	-1.940061000
F	0.438321000	2.682436000	-0.359606000

Zero-point correction= 0.118756
Thermal correction to Energy= 0.130596
Thermal correction to Enthalpy= 0.13154
Thermal correction to Gibbs Free Energy= 0.078494
Sum of electronic and zero-point Energies= -980.562306
Sum of electronic and thermal Energies= -980.550466
Sum of electronic and thermal Enthalpies= -980.549522
Sum of electronic and thermal Free Energies= -980.602567
SCF Energy -980.681062

TS1

C	1.521127000	-0.245636000	0.080157000
C	0.538094000	0.650126000	0.693713000
H	0.399851000	1.507957000	-0.243638000
C	-0.864180000	0.230683000	0.828139000
C	-1.430586000	-0.428809000	-0.417631000
H	-0.979106000	-1.404356000	-0.591329000
H	-1.194576000	0.216116000	-1.267560000
O	-1.556676000	0.513349000	1.790759000
O	1.327488000	-1.109913000	-0.755919000
O	2.772114000	0.054099000	0.520517000
C	3.822195000	-0.699352000	-0.089181000
H	3.708246000	-1.767750000	0.109042000
H	3.844973000	-0.541096000	-1.169990000
H	4.746934000	-0.337723000	0.357200000
Cl	-3.209931000	-0.648930000	-0.351805000

H 0.904641000 1.126395000 1.601738000
F 0.141618000 2.169989000 -1.314314000

Zero-point correction= 0.114119
Thermal correction to Energy= 0.125659
Thermal correction to Enthalpy= 0.126603
Thermal correction to Gibbs Free Energy= 0.074483
Sum of electronic and zero-point Energies= -980.564001
Sum of electronic and thermal Energies= -980.552462
Sum of electronic and thermal Enthalpies= -980.551518
Sum of electronic and thermal Free Energies= -980.603638
SCF Energy -980.67812

b

C 1.472268000 -0.273536000 0.204679000
C 0.513762000 0.597759000 0.805066000
H 0.456291000 1.587032000 -0.751356000
C -0.900009000 0.413025000 0.776080000
C -1.408736000 -0.645856000 -0.211657000
H -1.088913000 -1.648185000 0.071983000
H -1.039350000 -0.458170000 -1.219161000
O -1.696152000 1.072180000 1.450543000
O 1.284100000 -1.210558000 -0.566642000
O 2.754529000 0.080687000 0.569675000
C 3.780642000 -0.700891000 -0.027915000
H 3.696448000 -1.756801000 0.245394000
H 3.762638000 -0.624417000 -1.119108000
H 4.722269000 -0.302339000 0.349154000
Cl -3.209394000 -0.684629000 -0.314343000
H 0.881828000 1.307663000 1.540164000
F 0.409011000 1.961382000 -1.631039000

Zero-point correction= 0.117572
Thermal correction to Energy= 0.129591

Thermal correction to Enthalpy= 0.130535

Thermal correction to Gibbs Free Energy= 0.077321

Sum of electronic and zero-point Energies= -980.571639

Sum of electronic and thermal Energies= -980.55962

Sum of electronic and thermal Enthalpies= -980.558676

Sum of electronic and thermal Free Energies= -980.61189

SCF Energy -980.689211

c

C	0.404752000	-1.783775000	-0.016596000
C	0.089601000	-0.559602000	0.796686000
H	0.341797000	-0.750004000	1.840283000
C	-1.370104000	-0.133751000	0.788466000
C	-2.045328000	-0.047582000	-0.563697000
H	-2.264726000	-1.052177000	-0.926529000
H	-1.403947000	0.438010000	-1.299283000
O	-1.930978000	0.170234000	1.816132000
O	-0.114894000	-2.113797000	-1.061454000
O	1.404006000	-2.472267000	0.556571000
C	1.848098000	-3.626482000	-0.172961000
H	1.036709000	-4.347826000	-0.285668000
H	2.215978000	-3.339719000	-1.159952000
H	2.653607000	-4.057111000	0.417506000
Cl	-3.590396000	0.856184000	-0.505796000
C	1.210581000	0.825599000	-1.010432000
C	0.956186000	0.651102000	0.357887000
C	1.978056000	1.905802000	-1.437473000
H	2.188398000	2.044467000	-2.494558000
C	1.418830000	1.512772000	1.378627000
C	2.470980000	2.795538000	-0.486227000
H	3.074231000	3.645619000	-0.803613000
C	2.187851000	2.585138000	0.866670000
H	2.604955000	3.318323000	1.565440000
H	0.827657000	0.123384000	-1.750783000

Zero-point correction= 0.18531

Thermal correction to Energy= 0.199931

Thermal correction to Enthalpy= 0.200875

Thermal correction to Gibbs Free Energy= 0.140973

Sum of electronic and zero-point Energies= -1111.028798

Sum of electronic and thermal Energies= -1111.014176

Sum of electronic and thermal Enthalpies= -1111.013232

Sum of electronic and thermal Free Energies= -1111.073135

SCF Energy -1111.214108

d

C	0.042018000	-1.835640000	0.058438000
C	-0.061191000	-0.353039000	0.282062000
H	-0.350532000	-0.186109000	1.344090000
C	-1.237987000	0.186385000	-0.549395000
C	-2.477444000	0.276984000	0.282838000
H	-2.207936000	0.822658000	1.211099000
H	-2.773732000	-0.732308000	0.585506000
O	-1.135469000	0.533212000	-1.701370000
O	-0.838489000	-2.527019000	-0.407268000
O	1.212518000	-2.322684000	0.496489000
C	1.369251000	-3.743454000	0.366479000
H	0.608931000	-4.271122000	0.945269000
H	1.299251000	-4.044963000	-0.680345000
H	2.359847000	-3.968300000	0.755491000
Cl	-3.867254000	1.031515000	-0.556219000
C	2.014522000	0.227339000	-1.066903000
C	1.185859000	0.453345000	0.034697000
C	3.129581000	1.030467000	-1.281557000
H	3.772218000	0.844467000	-2.136915000
C	1.476594000	1.505359000	0.906794000
C	3.423064000	2.071899000	-0.403126000
H	4.295167000	2.696176000	-0.572201000
C	2.592958000	2.308053000	0.689444000
H	2.815877000	3.120575000	1.374928000

H	1.789588000	-0.582979000	-1.755539000
H	0.792769000	1.659009000	1.742368000
F	-1.034440000	0.985875000	2.624504000

Zero-point correction= 0.199829
Thermal correction to Energy= 0.216331
Thermal correction to Enthalpy= 0.217275
Thermal correction to Gibbs Free Energy= 0.153265
Sum of electronic and zero-point Energies= -1211.56347
Sum of electronic and thermal Energies= -1211.546968
Sum of electronic and thermal Enthalpies= -1211.546024
Sum of electronic and thermal Free Energies= -1211.610034
SCF Energy -1211.763299

TS2

C	0.215880000	1.671105000	-0.116729000
C	0.117252000	0.227042000	0.174202000
H	0.341707000	0.211661000	1.418312000
C	1.233147000	-0.647659000	-0.265485000
C	2.628487000	-0.043733000	-0.199913000
H	2.788941000	0.461355000	0.752634000
H	2.778138000	0.685596000	-0.994334000
O	1.065210000	-1.818046000	-0.558474000
O	1.234951000	2.314478000	-0.293276000
O	-1.001978000	2.265108000	-0.082016000
C	-0.988827000	3.683468000	-0.263931000
H	-0.412152000	4.175089000	0.522805000
H	-0.565938000	3.951915000	-1.234538000
H	-2.029505000	3.998484000	-0.213339000
Cl	3.916491000	-1.287894000	-0.369828000
C	-1.859338000	-0.462102000	-1.252911000
C	-1.233193000	-0.411581000	-0.003726000
C	-3.094609000	-1.080899000	-1.405842000
H	-3.568281000	-1.110353000	-2.382893000
C	-1.871120000	-1.003710000	1.087868000

C	-3.724938000	-1.665863000	-0.308304000
H	-4.689618000	-2.149746000	-0.427411000
C	-3.108554000	-1.625695000	0.938325000
H	-3.591930000	-2.079645000	1.798653000
H	-1.370340000	-0.008299000	-2.111815000
H	-1.372087000	-0.958258000	2.052074000
F	0.537794000	0.086872000	2.697304000

Zero-point correction= 0.19447
Thermal correction to Energy= 0.210743
Thermal correction to Enthalpy= 0.211687
Thermal correction to Gibbs Free Energy= 0.147699
Sum of electronic and zero-point Energies= -1211.562583
Sum of electronic and thermal Energies= -1211.54631
Sum of electronic and thermal Enthalpies= -1211.545365
Sum of electronic and thermal Free Energies= -1211.609354
SCF Energy -1211.757053

e

C	0.227869000	1.630294000	-0.193315000
C	0.072144000	0.198533000	-0.160333000
H	0.459527000	0.229934000	1.688317000
C	1.199392000	-0.683477000	-0.338535000
C	2.591015000	-0.038225000	-0.366901000
H	2.769658000	0.584431000	0.508331000
H	2.737208000	0.582576000	-1.249022000
O	1.101871000	-1.909607000	-0.433462000
O	1.261740000	2.271232000	-0.362947000
O	-0.950380000	2.291878000	0.061197000
C	-0.848006000	3.710858000	0.071643000
H	-0.169529000	4.058645000	0.855558000
H	-0.495159000	4.096561000	-0.888809000
H	-1.853627000	4.081857000	0.267621000
Cl	3.906574000	-1.278641000	-0.390618000
C	-2.301818000	0.004309000	-1.009835000

C	-1.275630000	-0.423168000	-0.153033000
C	-3.552884000	-0.603320000	-1.005463000
H	-4.324501000	-0.247447000	-1.682594000
C	-1.561881000	-1.499843000	0.701904000
C	-3.816400000	-1.668147000	-0.147179000
H	-4.792002000	-2.144524000	-0.143968000
C	-2.809739000	-2.113241000	0.706494000
H	-2.998862000	-2.940167000	1.385395000
H	-2.111789000	0.829411000	-1.689063000
H	-0.786997000	-1.853433000	1.374340000
F	0.700454000	0.238177000	2.607047000

Zero-point correction= 0.198142
Thermal correction to Energy= 0.214833
Thermal correction to Enthalpy= 0.215777
Thermal correction to Gibbs Free Energy= 0.151544
Sum of electronic and zero-point Energies= -1211.571905
Sum of electronic and thermal Energies= -1211.555214
Sum of electronic and thermal Enthalpies= -1211.55427
Sum of electronic and thermal Free Energies= -1211.618503
SCF Energy -1211.770047

f

C	-0.275563000	1.632398000	0.065567000
C	-0.124660000	0.210076000	-0.004131000
H	2.064349000	0.906571000	-1.484824000
C	-1.265365000	-0.654208000	-0.070010000
C	-2.651457000	0.011354000	-0.079398000
H	-2.802418000	0.645821000	-0.950875000
H	-2.827893000	0.623906000	0.802926000
O	-1.201499000	-1.889994000	-0.131881000
O	-1.315707000	2.289478000	0.001872000
O	0.922259000	2.292307000	0.264586000
C	0.818049000	3.706228000	0.338600000
H	0.399884000	4.131781000	-0.578500000

H	0.194888000	4.024072000	1.179811000
H	1.834088000	4.075312000	0.479996000
Cl	-3.987347000	-1.215172000	-0.116240000
C	1.504575000	-1.535221000	0.786325000
C	1.214645000	-0.415730000	-0.014631000
C	2.755600000	-2.142443000	0.769539000
H	2.942957000	-3.000100000	1.410374000
C	2.250788000	0.051309000	-0.843385000
C	3.768054000	-1.656024000	-0.054471000
H	4.744919000	-2.129735000	-0.068782000
C	3.503462000	-0.551552000	-0.861456000
H	4.276157000	-0.160751000	-1.518230000
H	0.728779000	-1.930406000	1.432283000

Zero-point correction= 0.186277
Thermal correction to Energy= 0.200438
Thermal correction to Enthalpy= 0.201382
Thermal correction to Gibbs Free Energy= 0.143943
Sum of electronic and zero-point Energies= -1111.10857
Sum of electronic and thermal Energies= -1111.094409
Sum of electronic and thermal Enthalpies= -1111.093465
Sum of electronic and thermal Free Energies= -1111.150904
SCF Energy -1111.294847

TS3

C	-0.262519000	1.565002000	0.056651000
C	0.018260000	0.185361000	-0.010316000
H	2.308282000	1.189598000	-1.116652000
C	-1.164350000	-0.620548000	-0.099360000
C	-2.456805000	0.202821000	-0.065453000
H	-2.895041000	0.593065000	-0.970941000
H	-2.876881000	0.546862000	0.866489000
O	-1.192386000	-1.846821000	-0.209041000
O	-1.439886000	1.999657000	0.014666000
O	0.760595000	2.429466000	0.201315000

Cl	-4.168933000	-1.381840000	-0.075855000
C	1.607185000	-1.651219000	0.590579000
C	1.361720000	-0.402874000	-0.013719000
C	2.874825000	-2.220770000	0.589720000
H	3.027394000	-3.182231000	1.072490000
C	2.457324000	0.234552000	-0.626581000
C	3.946697000	-1.568620000	-0.015008000
H	4.936548000	-2.014302000	-0.014572000
C	3.725109000	-0.335280000	-0.622546000
H	4.545288000	0.186486000	-1.107918000
H	0.785179000	-2.174511000	1.062716000
C	0.398673000	3.810932000	0.295757000
H	-0.228629000	3.995046000	1.170694000
H	1.336913000	4.354061000	0.393521000
H	-0.130480000	4.142648000	-0.600166000

Zero-point correction= 0.185017
Thermal correction to Energy= 0.19893
Thermal correction to Enthalpy= 0.199874
Thermal correction to Gibbs Free Energy= 0.142648
Sum of electronic and zero-point Energies= -1111.088938
Sum of electronic and thermal Energies= -1111.075024
Sum of electronic and thermal Enthalpies= -1111.07408
Sum of electronic and thermal Free Energies= -1111.131306
SCF Energy -1111.273955

g

C	0.219145000	1.564592000	-0.023116000
C	0.402290000	0.193339000	0.003067000
H	2.948326000	1.154733000	0.376008000
C	-0.929949000	-0.363856000	0.018539000
C	-1.879286000	0.816888000	0.010989000
H	-2.521581000	0.834003000	-0.871645000
H	-2.499238000	0.862993000	0.908493000
O	-1.313303000	-1.528033000	0.037865000

O	-1.039280000	1.991808000	-0.020177000
O	1.150402000	2.482205000	-0.059601000
Cl	-5.793427000	-1.190918000	0.042487000
C	1.661086000	-1.936446000	-0.188436000
C	1.662774000	-0.542707000	0.007810000
C	2.846126000	-2.661428000	-0.186752000
H	2.812580000	-3.735757000	-0.342967000
C	2.905361000	0.085458000	0.211741000
C	4.068026000	-2.024624000	0.011131000
H	4.992585000	-2.593056000	0.011262000
C	4.085890000	-0.646899000	0.210975000
H	5.029276000	-0.133401000	0.371717000
H	0.713295000	-2.439552000	-0.334715000
C	0.735482000	3.867522000	-0.103158000
H	0.162054000	4.120404000	0.788747000
H	1.660353000	4.437013000	-0.130562000
H	0.146399000	4.059350000	-1.000051000

Zero-point correction= 0.188225
Thermal correction to Energy=0.202649
Thermal correction to Enthalpy=0.203593
Thermal correction to Gibbs Free Energy=0.142966
Sum of electronic and zero-point Energies= -1111.134179
Sum of electronic and thermal Energies=-1111.119755
Sum of electronic and thermal Enthalpies=-1111.118811
Sum of electronic and thermal Free Energies=-1111.179438
SCF Energy -1111.322404

3.7.4 Single crystal X-ray data of 68a

Crystal data: $C_{12}H_{12}O_3$, M_r = 204.22, monoclinic, space group *C*2/*c*, *a* = 15.6759, *b* = 7.2560(2), *c* = 19.3615(5) Å, β = 111.935(4)°, *V* = 2042.82 Å^3, *Z* = 8, *T* = 100 K, D_x = 1.328 Mg m^{-3}, μ = 0.095 mm^{-1}, *F*(000) = 864. *Data collection*: A colourless block 0.4 × 0.25 × 0.15 mm was mounted on a glass fibre in inert oil and transferred to the cold gas stream of an Oxford Diffraction Xcalibur E diffractometer. Measurements were performed using monochromated

Mo *K*α radiation (λ = 0.71073 Å). A total of 47291 intensities were registered to $2\theta_{max}$ = 61.7°, of which 3099 were independent (R_{int} = 0.024). No absorption correction was applied, but appropriate frame scaling was performed. *Structure refinement*: The structure was refined anisotropically using the program SHELXL-97 (G. M. Sheldrick, University of Göttingen, Germany). Hydrogen atoms were included using a rigid methyl group allowed to rotate but not tip, and a riding model for all other hydrogens. The final *wR*2 value was 0.099 for all reflections and 137 parameters, with a corresponding *R*1 of 0.036 for reflections with $F > 4\sigma(F)$. The GOOF was 1.05; residual electron density was 0.40 e $Å^{-3}$.

Complete crystallographic data have been deposited at the Cambridge Crystallographic Data Centre as CCDC-1891729. These can be obtained free of charge from www.ccdc.cam.ac.uk/data_request/cif.

The molecular structure is shown in Fig. S1. The two rings subtend an interplanar angle of 9.26(4)°. The ethoxy group is essentially coplanar with the five-membered ring; C6 lies 0.060(2) and C7 0.073(2) Å out of the plane. The packing features a "weak" but short hydrogen bond H2A···O2 (2.30 Å, 170°; operator *–x*, 1*–y*, 1*–z*) and an H···π contact H6B···$Cent_{phenyl}$ 2.65 Å, 149°, operator 0.5*–x*, 1.5*–y*, 1*–z*).

3.8. References

(1) Biju, A. T. Modern aryne chemistry, Wiley-VCH: Weinheim, **2020**

(2) R. Sanz, Org. Prep. Proced. Int. **2008**, 40, 215.

(3) Y. Chen, R. C. Larock, In *Modern Arylation Methods*; Ackermann, L., Ed.; Wiley-VCH: Weinheim, **2009**;

(4) K. Okuma, *Heterocycles* **2012**, *85*, 515.

(5) A. V. Dubrovskiy, N. A. Markina, R. C. Larock, *Org. Biomol. Chem.* **2013**, *11*, 191.

(6) C. Wu, F. Shi, *Asian J. Org. Chem.* **2013**, 2, 116.

(7) S. S. Bhojgude, A. T. Biju, *Angew. Chem., Int. Ed.* **2012**, *51*, 1520.

(8) A. Bhunia, S. R. Yetra, A. T. Biju, *Chem. Soc. Rev.* **2012**, *41*, 3140.

(9) S. S. Bhojgude, A. Bhunia, A. T. Biju, *Acc. Chem. Res.* **2016**, *49*, 1658.

(10) Y. Himeshima, T. Sonoda, H. Kobayashi, *Chem. Lett.* **1983**, *12*, 1211.

(11) Y. Himeshima, T. Sonoda, H. Kobayashi, *Chem. Lett.* **1983**, *12*, 1211.

(12) W. G. Shou, Y. Y. Yang, Y. G. Wang, *J. Org. Chem.*, **2006**, *71*, 9241.

(13) C. Xie, Y. Zhang, *Org. Lett.,* **2007**, *9*, 781.

(14) T. Hamura, T. Hosoya, H. Yamaguchi, Y. Kuriyama, M. Tanabe, M. Miyamoto, Y. Yasui,
T. Matsumoto and K. Suzuki, *Helv. Chim. Acta*, **2002**, *85*, 3589.
(15) J. B. Feltenberger, R. Hayashi, Y. Tang, E. S. C. Babiash and R. P. Hsung, *Org. Lett.,* **2009**,
11, 3666.
(16) F. Shi, R. Mancuso and R. C. Larock, *Tetrahedron Lett.*, **2009**, *50*, 4067
(17) A. Kivrak and R. C. Larock, *J. Org. Chem*., **2010**, *75*, 7381
(18) C. Spiteri, S. Keeling and J. E. Moses, *Org. Lett*., **2010**, *12*, 3368.
(19) J. Zhao, C. Wu, P. Li, W. Ai, H. Chen, C. Wang, R. C. Larock and F. Shi, *J. Org. Chem.,* **2011**, *76*, 6837
(20) H. Yoshida, H. Fukushima, J. Ohshita, A. Kunai, *Angew. Chem., Int. Ed.*, **2004**, *116,* 4025.
(21) H. Yoshida, H. Fukushima, J. Ohshita, A. Kunai, *Tetrahedron Lett.*, **2004**, 45, 8659.
(22) H. Yoshida, H. Fukushima, J. Ohshita, A. Kunai, *J. Am. Chem. Soc.*, **2006**, *128*, 11040.
(23) M. Jeganmohan, C.-H. Cheng, *Chem. Commun.,* **2006**, 2454
(24) M. Jeganmohan, S. Bhuvaneswari, C.-H. Cheng, *Chem.–Asian. J.*, **2010**, *5*, 153.
(25) a) C. Xie, Y. Zhang, P. Xu, *Synlett*, **2008**, 3115. b) X. Huang, T. Zhang, *Tetrahedron Lett.,*
2009, *50*, 208.
(26) E. Yoshioka, S. Kohtani, H. Miyabe, Angew. *Chem., Int. Ed*., **2011**, *50*, 6638.
(27) H. Yoshida, Y. Ito, J. Ohshita, *Chem. Commun*., **2011**, *47*, 8512.
(28) H. Yoshida, E. Shirakawa, Y. Honda, T. Hiyama, *Angew. Chem., Int. Ed.,* **2002**, 41, 3247
(29) U. K. Tambar, B. M. Stoltz, *J. Am. Chem. Soc.*, **2005**, *127*, 5340.
(30) H. Yoshida, M. Watanabe, J. Ohshita, A. Kunai, *Tetrahedron Lett*., **2005**, *46*, 6729
(31) H. Yoshida, M. Watanabe, T. Morishita, J. Ohshita, A. Kunai, *Chem. Commun*., **2007**, 1505.
(32) H. Yoshida, T. Kishida, M. Watanabe, J. Ohshita, *Chem. Commun.,* **2008**, 5963.
(33) Y.-L. Liu, Y. Liang, S.-F. Pi and J.-H. Li, *J. Org. Chem*., **2009**, *74*, 569.
(34) Z. Liu, R. C. Larock, *Org. Lett.*, **2003**, *5,* 4673
(35) Z. Liu, R. C. Larock, *Org. Lett.*, **2004**, *6*, 99
(36) J. Zhao, R. C. Larock, *Org. Lett*., **2005**, *7,* 4273.
(37) Y. K. Ramtohul, A. Chartrand, *Org. Lett*., **2006**, *9*, 1029.

(38) F. S. Pashkovskii, E. M. Shchukina, M. G. Gribovskii, F. A. Lakhvich, *Russ. J. Org. Chem.*

2006, *42*, 527.

(39) Y. Zhao, D. G. Truhlar, *J. Chem. Phys.* **2006**, *125* 194101.

(40) A. V. Marenich, C. J. Cramer, D. G. Truhlar, *J. Phys. Chem. B*, **2009**, *113*, 6378.

(41) K. Remya, C. H. Suresh, *J. Comput. Chem.* **2013**, *34*, 1341.

(42) Gaussian 16, Revision A.03, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A. V.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov, A. F.; Sonnenberg, J. L.; Williams-Young, D.; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M. J.; Heyd, J. J.; Brothers, E. N.; Kudin, K. N.; Staroverov, V. N.; Keith, T. A.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A. P.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B.; Fox, D. J. Gaussian, Inc., Wallingford CT, 2016.

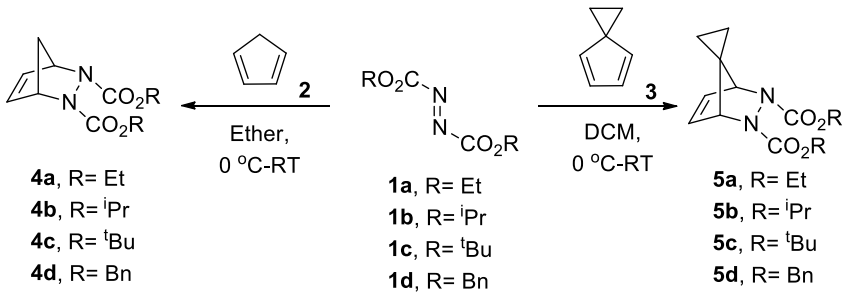
CHAPTER 4

Palladium Catalyzed Desymmetrization of Diazabicylic Olefins with 4-Halo-1,3-dicarbonyl compounds: Accessing 3(2*H*)-Furanone Appended Cyclopentenes

4.1 Introduction

Bicyclic alkenes, such as oxa, aza and diaza norbornadienes and their derivatives are considered as versatile synthons in synthetic organic chemistry. They can be readily activated by transition metal complexes due to their bicyclic structure, intrinsic strain on the carbon–carbon double bond and the eclipsing interactions. The instability of diazanorbornadienes make them suitable candidates for the synthesis of different functionalized carbocycles and heterocycles in stereo- and chemo-selective manner.[1]

Diazanorbornenes can be easily prepared *via* Diels-Alder reaction of cyclopentadiene derivatives and the corresponding dialkylazodicarboxylates in quantitative yields. (Scheme 4.1).[2]



Scheme 4.1

The strained diazanorbornenes possess different modes of reactivity (Fig.4.1). Their desymmetrization can be achieved through

(i) Electrophilic additions across the double bond

(ii) C=C bond cleavage

(iii) N-N bond cleavage and

(iv) Allylic fragmentation

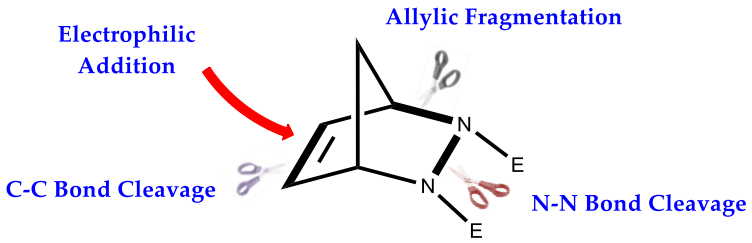


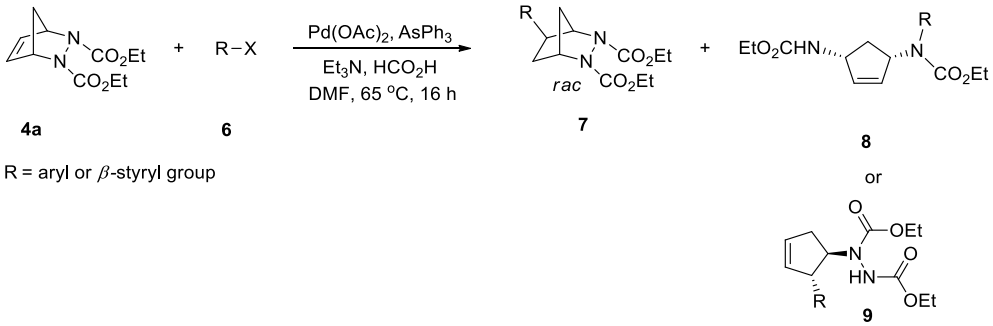
Figure 4.1 General reactivity pattern of diazanorbornenes.

Transition metals like palladium, rhodium, nickel, copper etc. have been extensively employed for the ring opening reactions of these strained systems. The ring opening reactions of diazabicyclic olefins can generate functionalized cyclopentenes or cyclopentannulated heterocycles with multiple stereocentres. Initially the desymmetrization reactions were focused on the transformations without ring fragmentation, later different approaches with mono- and bi-centred nucleophiles have been developed *via* ring opening chemistry. Various transition metal catalysed protocols were reported in literature for desymmetrisation reactions, but in this chapter, we are mainly focusing on palladium catalysed strategies. Hence a brief discussion on the synthetic transformations of diazanorbornenes under transition metal catalysis is presented below.

4.2 Transformations of diazabicyclic olefins without ring fragmentation

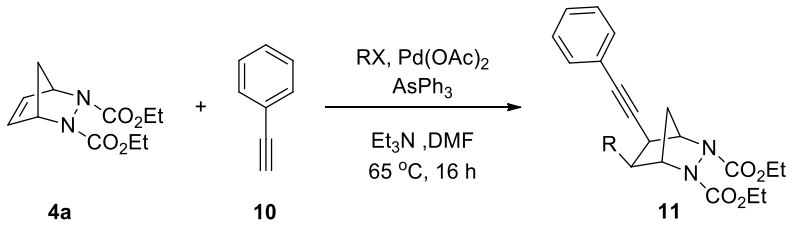
4.2.1 Hydroarylation reactions

The chemistry of desymmetrization of diazabicyclic olefins under palladium-catalysis without ring opening was first reported by Kauffmann and co-workers (scheme 4.2). They developed the hydroarylation of the diazabicyclic olefins **4** with organic halides *via* coupling reactions from which *exo*-configured hydroarylation and hydrovinylation products were formed exclusively in good yields. They have also observed the formation of a side product *via* the N-N bond cleavage of diazabicyclic olefin.[3]



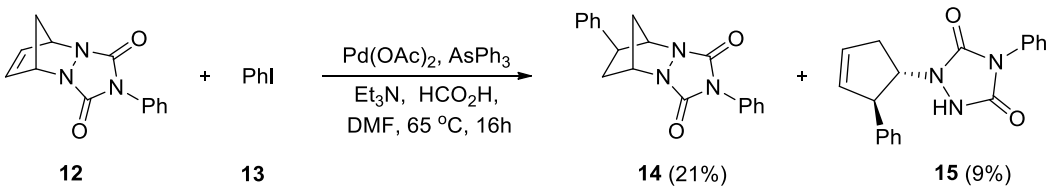
Scheme 4.2

They extended the same protocol of hydroarylation with aryl halide and phenylacetylene **10** with the bicyclic alkene **4a**, which resulted in the formation of a bis-coupled product **11**. In this case, they did not observe the formation of the ring opened product (Scheme 4.3).



Scheme 4.3

They have also performed the hydroarylation of the sterically more hindered and more rigid, tri-or tetracyclic Diels-Alder adducts **12** (of 1,3-cyclopentadiene with very reactive azodienophiles 4-phenyl-1,2,4-triazoline-3,5-dione) and from this reaction**,** the hydroarylated product **14** was formed along with small amount of 3,4-disubstituted cyclopentene **15** (Scheme 4.4).[4]

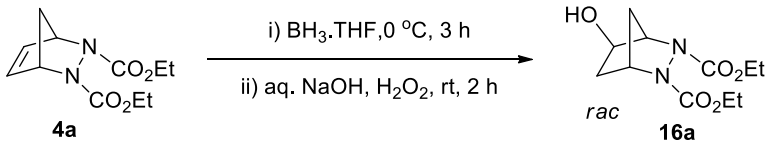


Scheme 4.4

4.2.2 Hydroboration reaction

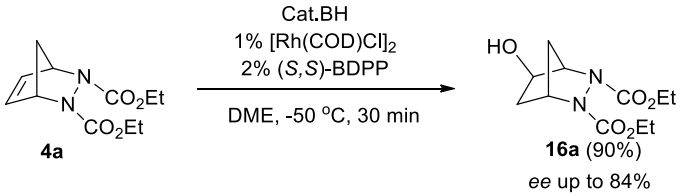
Other strategies reported for the desymmetrization of diazabicyclic olefins without ring opening includes hydroboration, amino hydroxylation, dihydroxylation and hydroformylation reactions.

The chemistry of diazabicyclic olefin transformations began with the hydroboration reaction performed by Allred and co-workers in 1966. The hydroboration of **4a** in THF at 0 °C followed by oxidation afforded the product **16a** as a racemic mixture (Scheme 4.5).[5]



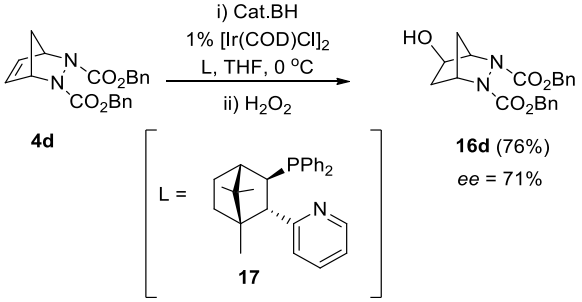
Scheme 4.5

Later, Micouin and co-workers reported the catalytic asymmetric hydroboration of diazabicyclic alkenes (Scheme 4.6). They developed an enantioselective hydroboration with $[Rh(COD)Cl]_2$ and (*S,S*)-BDPP with an *ee* of 84%. They also revealed that, the use of (*S,S*)-DIOP as ligand afforded the alcohol with inverse configuration.[6]



Scheme 4.6

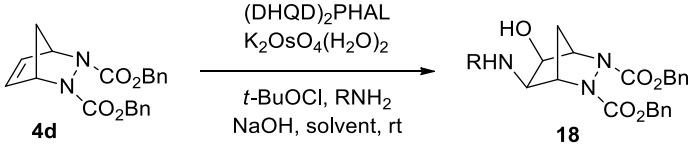
They also developed the first Iridium catalyzed asymmetric hydroboration (Scheme 4.7). A complete reversal in *ee* was observed upon switching from rhodium to iridium. These results helped them to show that Rh-catalyzed hydroboration involves a metal-H insertion, whereas a boryl migration occurs in the case of iridium. The chemical yield and enantioselectivity of iridium based desymmetrization was increased by using commercially available (*R,S*)-Josiphos ligand.[7]



Scheme 4.7

4.2.3 Aminohydroxylation reaction

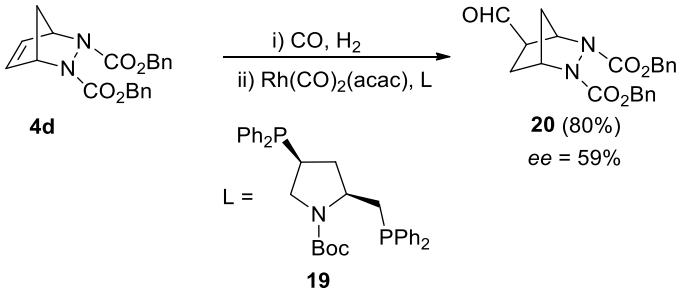
Micouin *et al.* reported the first asymmetric aminohydroxylation of bicyclic olefin **4d** in 2009. They synthesized the aminoalcohols **18** in 30-78% yield. The relative steric barrier of the substrate, which barely fits into the binding pocket of the chiral catalyst, can be used to explain this poor selectivity (Scheme 4.8).[8]



Scheme 4.8

4.2.4 Hydroformylation reaction

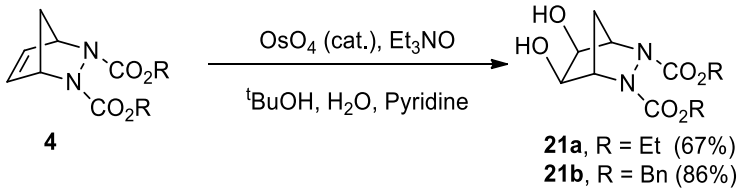
In 2008, Micouin *et al*. carried out the asymmetric hydroformylation of bicyclic olefin **4d** and the aldehyde **20** was obtained in good yield. The asymmetric transformation was done with the combination of $Rh(CO)_2(acac)$ and diphosphine ligand **19** which enabled the hydroformylation to proceed with excellent conversion and moderate enantioselectivities up to 59% (Scheme 4.9).[9]



Scheme 4.9

4.2.5 Dihydroxylation reaction

The dihydroxylation of bicyclic olefin **4** using osmium tetroxide for the generation of *exo*-dihydroxylated product **21** was reported by Meller and coworkers in 1984 (Scheme 4.10).[10]



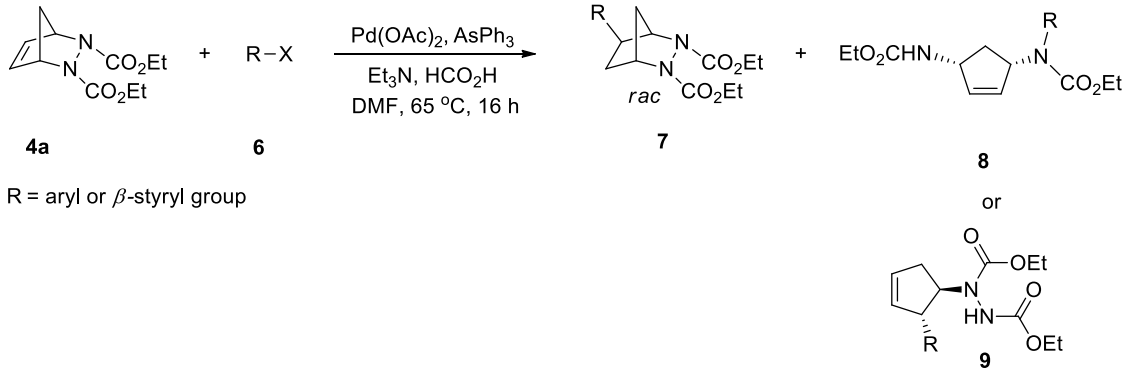
Scheme 4.10

4.3 Transformations of diazabicyclic olefins through palladium catalyzed ring opening reactions

4.3.1 Palladium catalyzed ring opening reactions with mono-centered reactive species

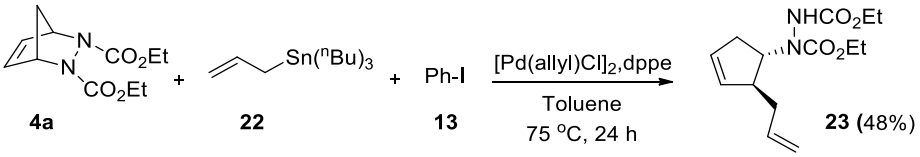
Desymmetrization of diazabicyclic olefins *via* ring opening reactions are considered as a valuable tool for the generation of functionalized cyclopentenes. Various groups have reported different strategies for the ring opening of bicyclic olefins with various nucleophiles like aryl iodides, soft nucleophiles and organometallic reagents such as organoboronic acids, organotin compounds, organogallium compounds, organoindium compounds, *etc*.

The first report on the ring opening of diazabicyclic olefin was reported by Kauffmann and co-workers when they worked on the hydroarylation of diazabicyclic alkenes. Along with the hydroarylated product a small amount of ring cleaved product was also identified (Scheme 4.2).



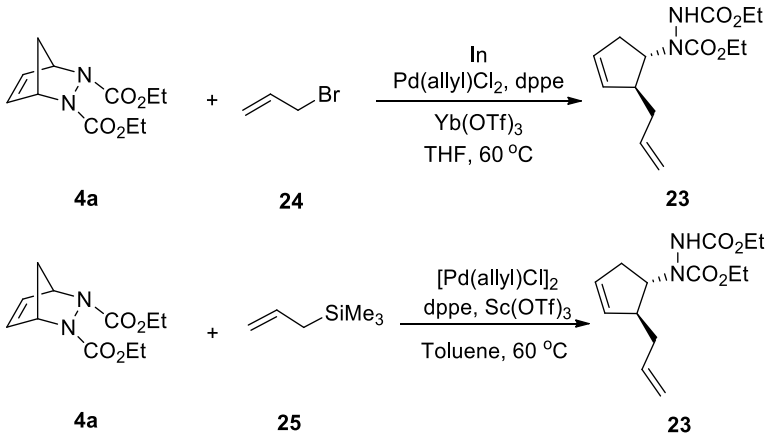
Scheme 4.2

The investigations on the palladium catalyzed ring opening of diazabicyclic olefins with organometallic reagents was pioneered by our group in 2005. When we worked on the bis-coupling reaction of diazabicyclic alkene **4a** with aryl iodide **13** and organostannanes **22**, we came across a serendipitous observation of the formation of allylated hydrazino cyclopentene **23** instead of domino Heck-Stille coupled product (Scheme 4.11).[11] The reaction is milder and is the first general methodology developed for the stereoselective synthesis of *trans*-vicinal disubstituted cyclopentenes.



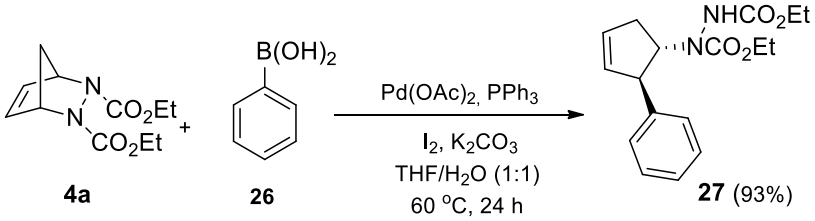
Scheme 4.11

Later the same chemistry was achieved with palladium/Lewis acid catalyzed reaction of organoindium and allyltrimethyl silane (Scheme 4.12).[12] A general observation was made such as, use of monocentered strong nucleophiles in the ring opening reaction of strained diazanorbornenes under palladium catalysis resulted in the formation of *trans*-vicinal disubstituted cyclopentenes.



Scheme 4.12

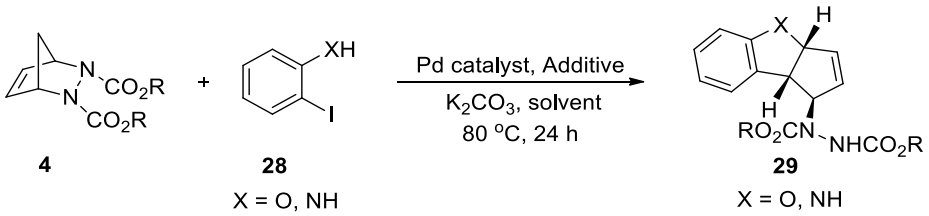
In 2006, we reported the reactivity of organoboronic acids **26** with bi- and tricyclic hydrazines which lead to the stereoselective formation of *trans*-vicinal disubstituted cyclopentenes in good to excellent yields (Scheme 4.13).[13] This palladium-catalyzed fragmentation is assisted by iodine, which proved to be superior to scandium triflate. This was the first report on the use of the modified Suzuki reaction for the synthesis of functionalized cyclopentenes.



Scheme 4.13

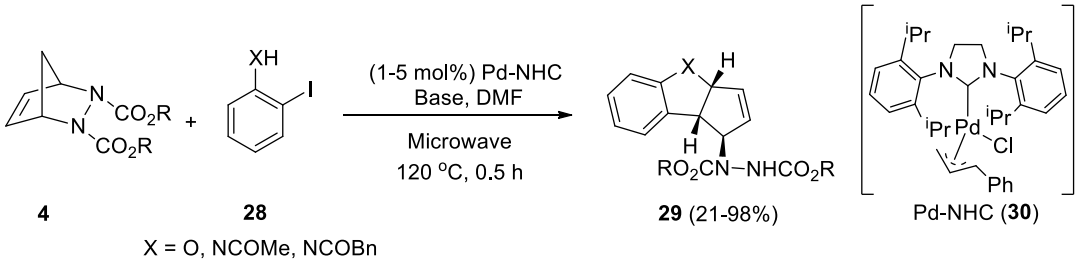
4.3.2 Palladium catalyzed ring-opening reactions with bi-centered reactive species

We have reported a palladium-catalyzed annulation of *o*-iodophenols and *o*-iodoanilines with diazabicyclic olefin (Scheme 4.14) in 2009.[14] The reaction afforded cyclopentene fused benzofuran and indoles **29**, through a tandem ring opening-ring closing pathway. In this reaction 2-iodophenol or 2-iodoaniline acts as the bicentered reactive species. Target molecules **29** are generated in good to excellent yields and that too with high *trans*-selectivity in a single transformation.[15]



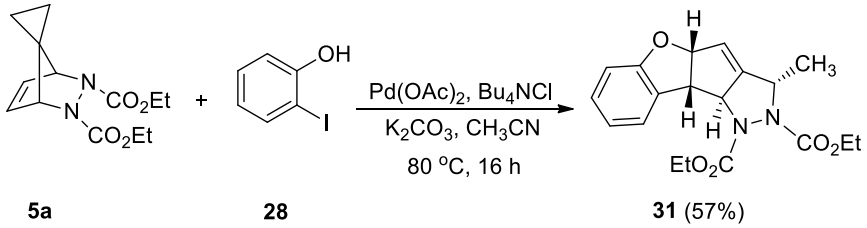
Scheme 4.14

Soon after our initial communication, Gilbertson *et al*. reported a palladium-*N*-heterocyclic carbene catalyzed version of the cyclopentannulation reaction (Scheme 4.15)[16]



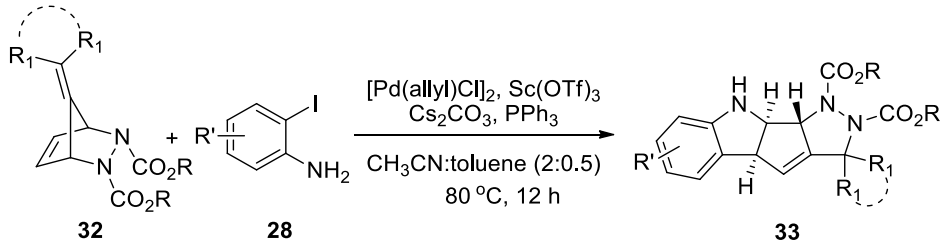
Scheme 4.15

In 2013, we reported an efficient one-pot strategy for the synthesis of a novel framework of benzofuran-pyrazolidine-fused cyclopentenes **31** by the palladium catalyzed tandem reaction of cyclopropane bearing spirotricyclic olefins with 2-iodophenols (Scheme 4.16).[17]

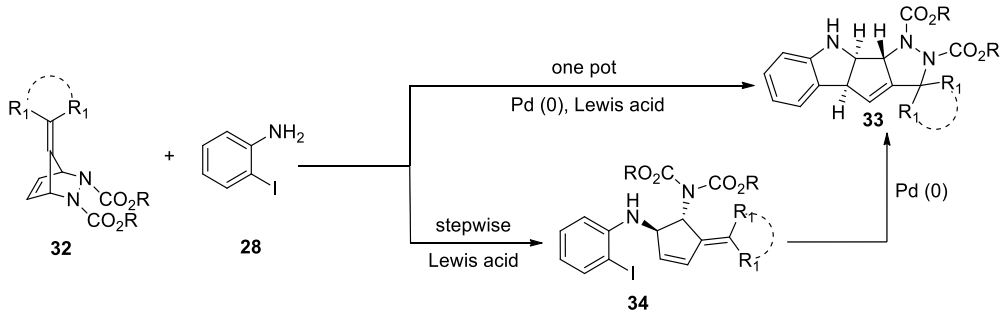


Scheme 4.16

Later our studies on the pentafulvene derived bicyclic hydrazines with o-iodoanilines under Lewis acid/palladium mediated transformation provided a new spiropentacyclic framework having cyclopentene fused to indoline and pyrazolidine skeletons **33** (Scheme 4.17). We have also tried the stepwise and one-pot transformation of pentafulvene derived diazabicyclic olefins with 2-iodoanilines in order to study the reaction pathway, and we found that Lewis acid mediated ring opening of **32** with **28** resulted in the formation of alkylidene cyclopentene moiety **34**, which upon palladium catalysed intramolecular heck reaction followed by rearrangements provided the cyclopentene fused to indoline and pyrazolidine skeletons (Scheme 4.18). [18]

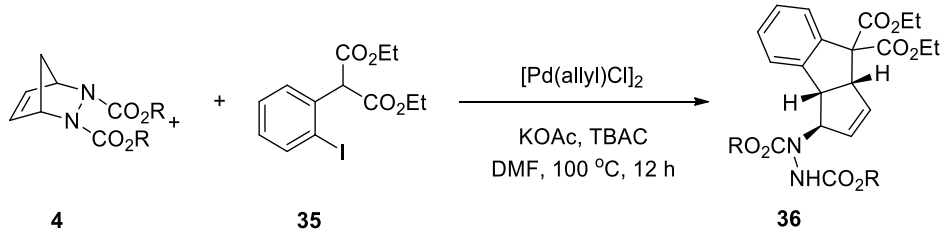


Scheme 4.17



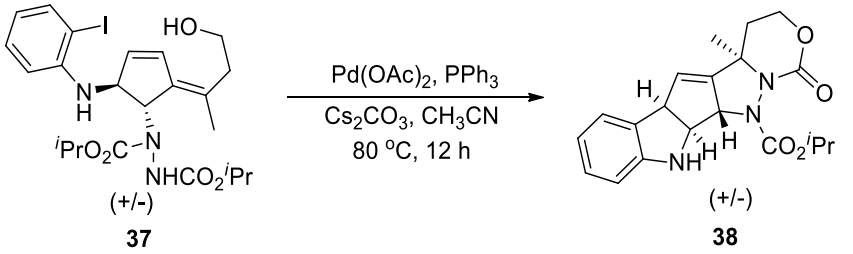
Scheme 4.18

An efficient one pot strategy for the synthesis of cyclopentene fused indanes **36** was reported from our laboratory (Scheme 4.19). The indane ring systems are very significant as they are important structural motifs in many drug candidates such as Gnetuhainin E and Mirabiloside C.[19]



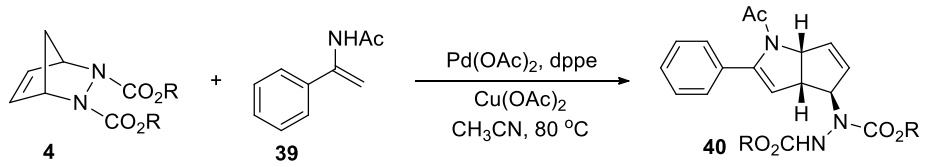
Scheme 4.19

The synthesis of polycyclic cyclopentene motifs with multiple stereocenters was also developed by our group. In this reaction, the strain release of fulvene derived diazanorbornenes with internal/external nucleophiles is efficiently exploited. In this line, a sequential Lewis acid/palladium mediated transformation of diazanorbornenes containing tethered hydroxy groups was reported. This tandem transformation transformation generated tetrahydrocyclopenta[*b*]pyrans or novel pentacyclic frameworks containing cyclopentene moieties fused to indoline, pyrazolidine, or 1,3-oxazinan-2-one skeletons (Scheme 4.20).[20]



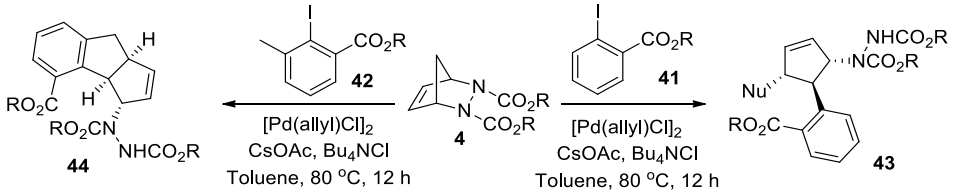
Scheme 4.20

Recently, a palladium catalyzed synthesis of cyclopentene fused 2-pyrrolines **40** from diazabicyclic olefin through alkenyl C-H activation of aromatic enamide **39** was reported by our group (Scheme 4.21).[21]



Scheme 4.21

We have also developed a Pd catalyzed cascade synthesis of the 3,4,5-trisubstituted cyclopentenes and indane fused cyclopentenes involving a novel benzylic C-H activation. The methodology is interesting for creating three adjacent stereocentres in a single transformation from simple and achiral diazabicyclic olefin (Scheme 4.22).[22]

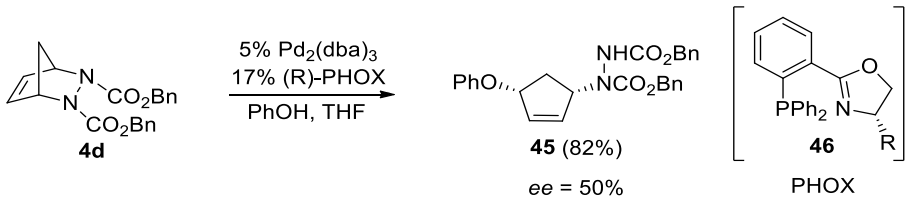


Scheme 4.22

4.3.3 Palladium catalyzed ring-opening reactions with soft nucleophiles

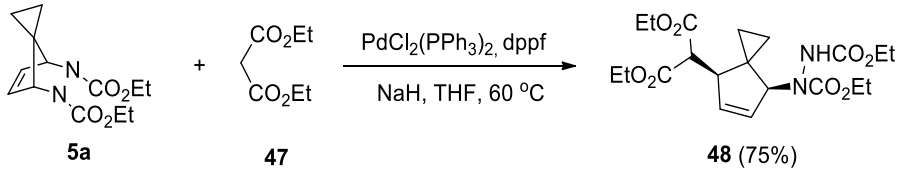
In 2003, Micouin and co-workers reported the use of nucleophiles such as phenol and active methylene compounds for trapping the π-allyl palladium species generated from diazabicyclic olefin under Pd-catalysis. They have shown that the treatment of alkene **4d** with a soft nucleophile in the presence of a palladium catalyst and ligand afforded the *cis*-3,5-disubstituted cyclopentene **45** in a diastereoselective manner. Several 'soft' nucleophiles like phenol, nitromethane and some active methylene compounds were successful in participating in this reaction (Scheme 4.22). They have also carried out the enantioselective version of this

transformation by employing chiral ligands. Among the various ligands examined, chiral PHOX ligands **46** gave better yields and enantioselectivity. The *cis*-stereochemistry of the product was explained on the basis of double inversion mechanism.[23]



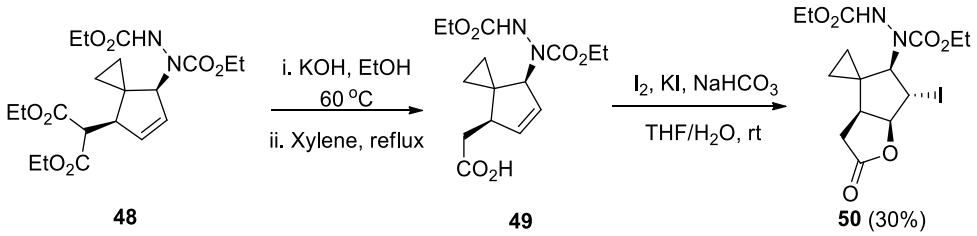
Scheme 4.22

Later our group also reported the palladium catalyzed ring opening methodologies of strained olefins with various soft nucleophiles. Reaction of spirotricyclic olefin **5a** with diethylmalonate **47** in the presence of $[Pd(allyl)Cl]_2$, dppf and NaH in THF at 60 ^oC afforded *cis*-4,7-disubstituted spiro[2.4]hept-5-ene **48** in 75% yield (Scheme 4.23).[24]



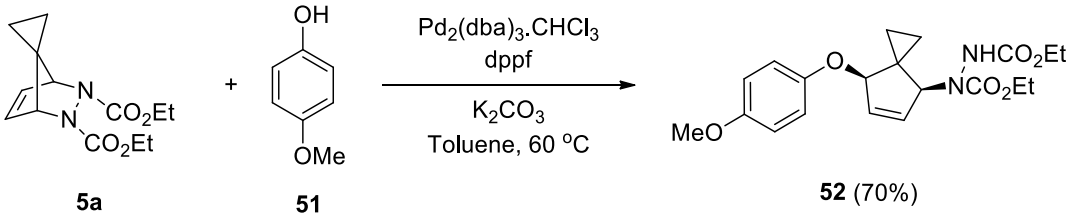
Scheme 4.23

In addition, *cis*-4,7-disubstitued spiro[2.4]heptenes obtained from various spirotricyclic olefins were transformed into iodolactones according to the previously reported literature (Scheme 4.24).



Scheme 4.24

Phenol also served as a soft nucleophile in the same ring-opening strategy of azabicyclic olefins and these reactions afforded the corresponding spiro[2.4]heptenes. Various spirotricyclic olefins and substituted phenols on treatment with palladium catalyst afforded the corresponding *cis*-disubstituted spiro[2.4]heptenes **52** (Scheme 4.25).[25]



5a **51** **52** (70%)

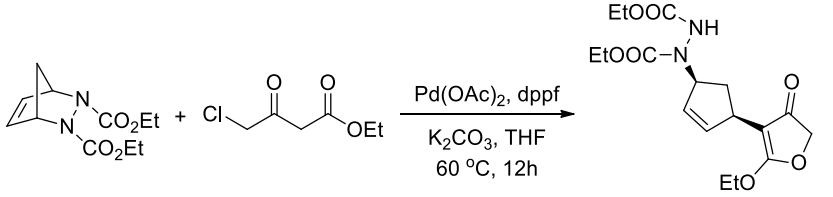
Scheme 4.25

4.4 Statement of the problem

In previous chapters, we have discussed the synthesis of substituted 3(2*H*)-furanones from 4-halo-1,3-dicarbonyl compounds with various electrophiles such as activated alkyne, benzyne *etc.* In this chapter, we hypothesized that 4-halo-1,3-dicarbonyl compounds could be used for trapping the π-allyl palladium intermediate generated from diazabicyclic olefins in the presence of Pd-catalyst for accessing 3(2*H*)-furanone appended hydrazino cyclopentenes. Desymmetrization of diazabicyclic olefins is an interesting and well explored area, while the reactivity of soft nucleophiles with the same is the least studied one. Since 4-halo-1,3-dicarbonyl compounds are soft nucleophiles, we can expect the same reactivity with diazabicyclic olefins as reported earlier. By employing carefully designed active methylene species, the ring-opening of diazabicyclic olefins could lead to the generation of 3(2*H*)-furanone substituted *cis*-disubstituted cyclopentenes which might be of biological significance.

4.5 Results and Discussion

We planned to assess our hypothesis by taking diazabicyclic olefin **4a** and ethyl-4-chloro acetoacetate **53a** as substrates. The initial reaction was set up with 1.0 equivalent of **4a** and 1.5 equivalents of **53a** in the presence of $Pd(OAc)_2$ as the catalyst, dppf as ligand and K_2CO_3 as base in THF at 60 ^oC (Scheme 4.26). After 12 h, we could isolate the expected 3(2*H*)-furanone appended hydrazino cyclopentene **54a** in 10% yield as a racemic mixture (Scheme 4.26). The structure of **54a** was assigned based on ^1H NMR, ^{13}C NMR, 2-D NMR, high resolution mass spectral analyses and on comparison with literature reports.[23-26]



4a **53a** **(±) 54a** (10%)

Scheme 4.26.

In the ^{1}H NMR spectrum (Fig. 4.2), the alkene protons in the cyclopentene moiety were found to resonate in between 5.57-5.65 ppm. The proton attached to the carbon bearing hydrazino moiety resonated at 5.32 ppm. The methylene proton in the furanone ring was found to be at 4.46 ppm and the proton at 1' position resonated in the range 3.40-3.42 ppm. The methylene protons in the cyclopente moiety resonated as two separate signals at 1.84 and 2.51 ppm respectively. In the ^{13}C NMR spectrum (Fig. 4.3), the furanone carbonyl resonated at 195.8 ppm and the C5 carbon resonated at 181.21 ppm. The ester carbonyls on the hydrazine moiety resonated at 156.8 and 156.1 ppm respectively. The alkene carbons resonated at 136.6 and 129.0 respectively. The C2 methylene carbon found at 74.7 ppm. All other signals in the ^{1}H and ^{13}C NMR spectra were in agreement with the proposed structure.

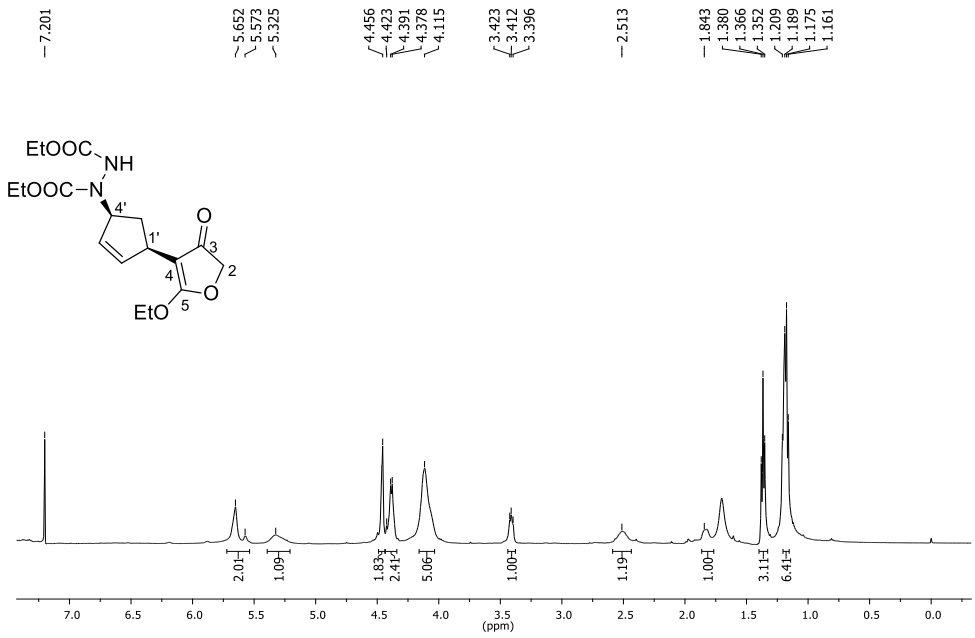


Figure 4.2. ^{1}H NMR spectrum of compound **54a**

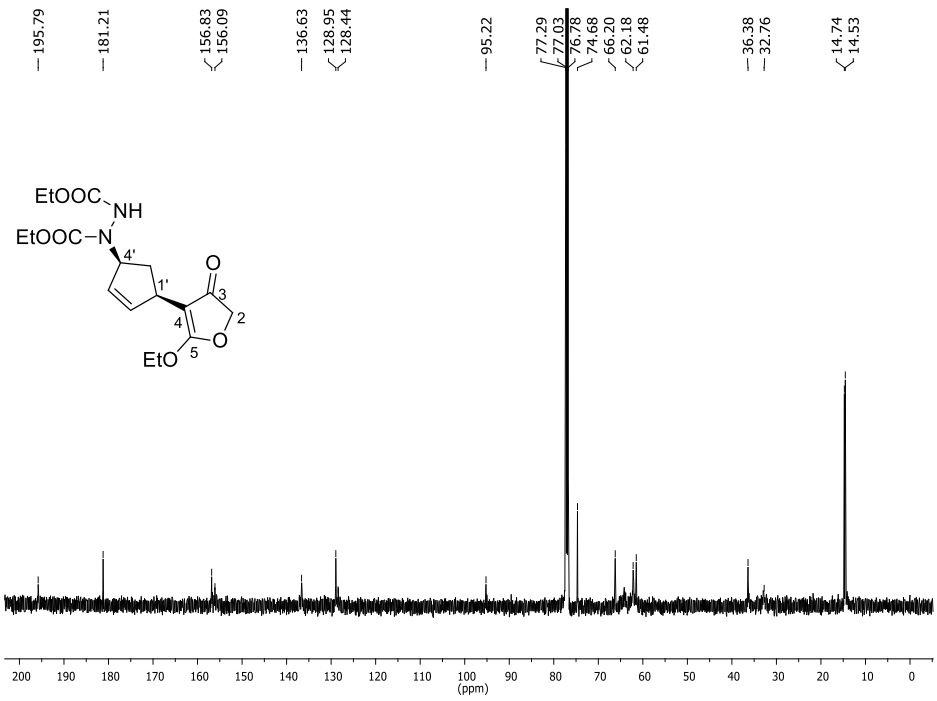


Figure 4.3. ^{13}C NMR spectrum of compound **54a**

The high resolution mass spectral analysis showed a peak at *m/z* 391.1492 $(M+Na)^+$, which also supported the proposed structure. In the HMBC spectrum (Fig. 4.4) the proton signal at 3.40-3.42 ppm (1') showed correlations with C5, C4 and C3 carbons. These relations confirmed the connectivity of cyclopentene moiety with 3(2*H*)-furanone core. All other HMBC correlations are also were in agreement with the proposed structure.

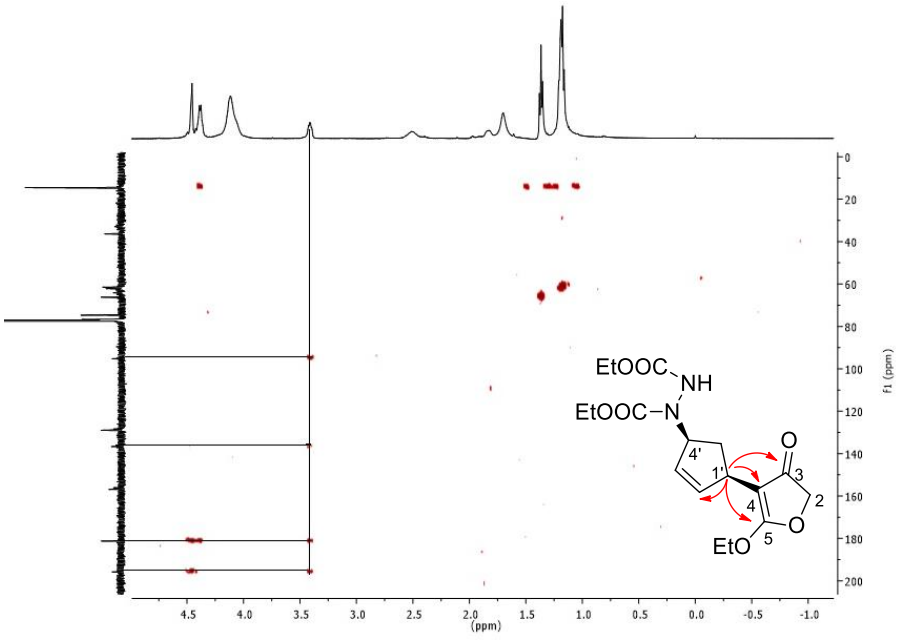


Figure 4.4. HMBC spectrum of compound **54a.**

The *cis* stereochemistry at the 1' and 4' positions are confirmed through the NOE analysis (Fig. 4.5) and in comparison, with the literature reports. When we irradiated the signal at 3.40-3.42 ppm, a signal enhancement in the opposite phase was observed at 5.32 ppm. This confirmed the stereochemistry of protons at 3.40-3.42 and 5.32 ppm as in the same phase or *cis*. The stereoselectivity in the desymmetrization of diazabicyclic olefins with soft nucleophiles under palladium catalysis can be explained on the basis of its double inversion mechanism.

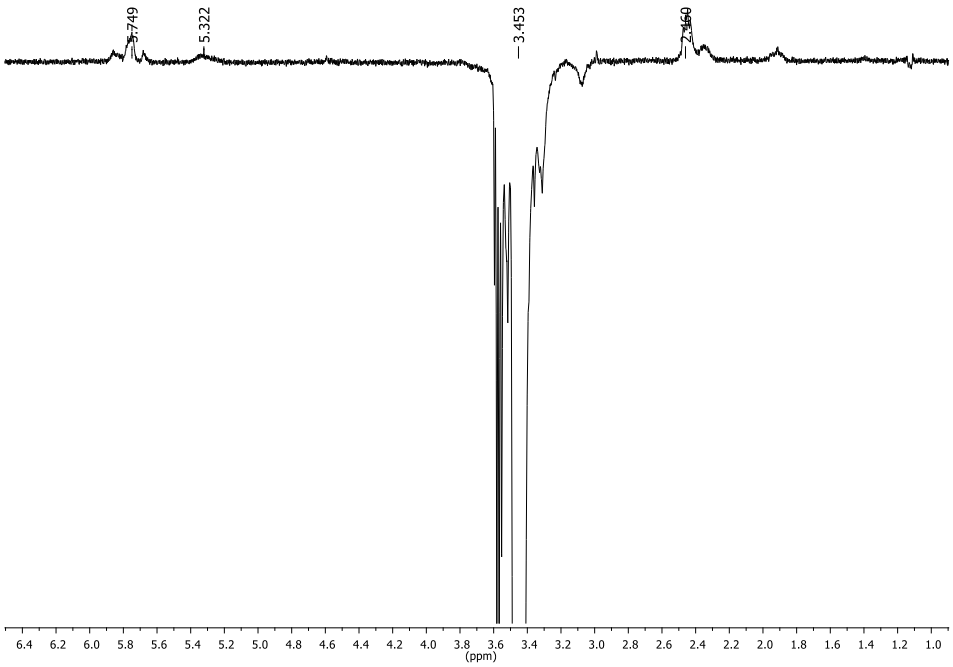
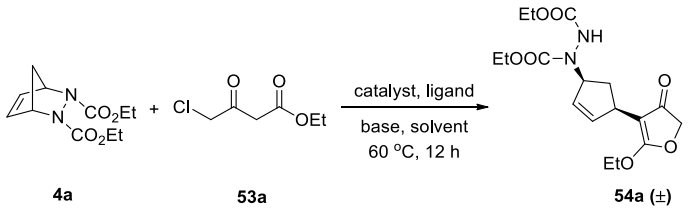


Figure 4.5. 1D-NOE spectrum of compound **54a.**

The optimization of the Pd-catalyzed ring opening of diazabicyclic olefin with 4-halo-1,3-dicarbonyl compounds was carried out with **4a** and **53a** as substrates. We started with the screening of Pd-catalysts such as $Pd(OAc)_2$, $Pd(OCOCF_3)_2$, $Pd(PPh_3)_4$, $(Pd(allyl)Cl)_2$, $PdCl_2$ and $Pd(dba)_3.CHCl_3$ among which the $(Pd(allyl)Cl)_2$ catalyzed reaction afforded the 3(2*H*)-furanone appended hydrazino cyclopentene **54a** in 32% yield (Table 4.1, entries 1-6). We then checked the efficiency of different ligands like dppf, dppe, dppp, XPhos and DevPhos from which XPhos was found to be the best option (Table 4.1, entries 4, 7-10). A base screen revealed that K_2CO_3 was superior to other bases like Na_2CO_3, Cs_2CO_3, NaH and NaO^tBu (Table 4.1, entries 9, 11-14). Finally, we examined different solvents such as THF, CH_3CN, toluene, 1,4-dioxane and DCE among which **54a** was isolated in 85% yield from the reaction with DCE as the medium (Table 4.1, entries 9, 15-18).

Table 4.1. Optimization studies



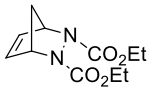
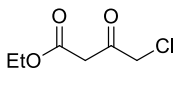
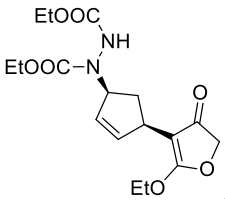
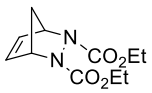
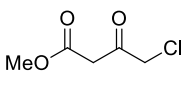
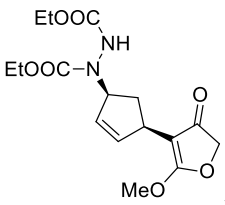
Entry	Catalyst	Ligand	Base	Solvent	Yield of 54a (%)
1	$Pd(OAc)_2$	dppf	K_2CO_3	THF	10
2	$Pd(OCOCF_3)_2$	dppf	K_2CO_3	THF	20
3	$Pd(PPh_3)_4$	dppf	K_2CO_3	THF	15
4	$(Pd(allyl)Cl)_2$	dppf	K_2CO_3	THF	32
5	$PdCl_2$	dppf	K_2CO_3	THF	28
6	$Pd(dba)_3.CHCl_3$	dppf	K_2CO_3	THF	23
7	$(Pd(allyl)Cl)_2$	dppe	K_2CO_3	THF	10
8	$(Pd(allyl)Cl)_2$	dppp	K_2CO_3	THF	34
9	$(Pd(allyl)Cl)_2$	XPhos	K_2CO_3	THF	55
10	$(Pd(allyl)Cl)_2$	DevPhos	K_2CO_3	THF	43
11	$(Pd(allyl)Cl)_2$	XPhos	Na_2CO_3	THF	51
12	$(Pd(allyl)Cl)_2$	XPhos	Cs_2CO_3	THF	32
13	$(Pd(allyl)Cl)_2$	XPhos	NaH	THF	NR
14	$(Pd(allyl)Cl)_2$	XPhos	NaO^tBu	THF	25
15	$(Pd(allyl)Cl)_2$	XPhos	K_2CO_3	CH_3CN	68

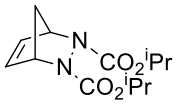
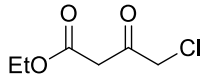
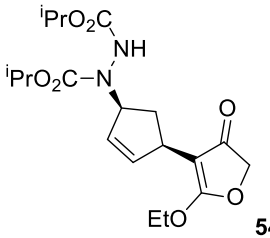
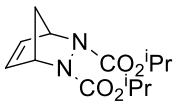
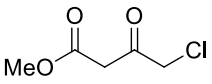
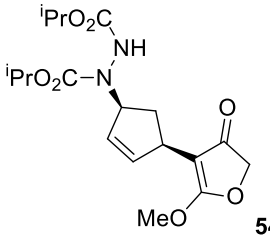
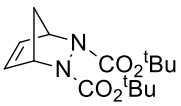
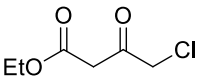
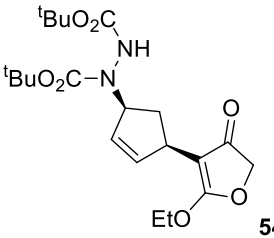
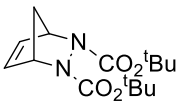
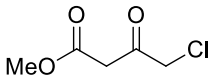
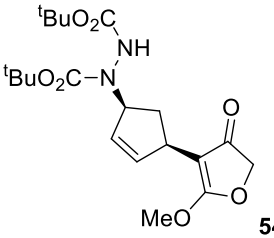
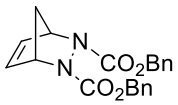
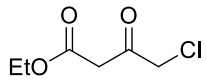
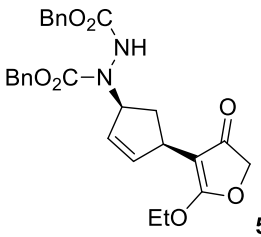
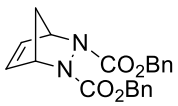
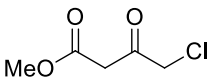
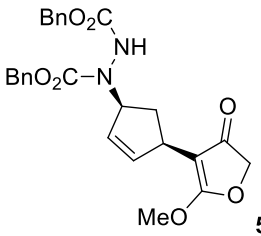
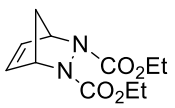
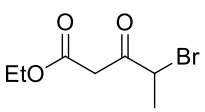
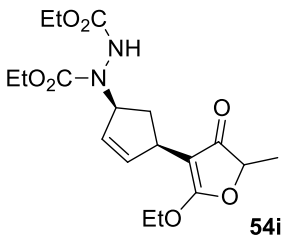
16	$(Pd(allyl)Cl)_2$	XPhos	K_2CO_3	Toluene	47
17	$(Pd(allyl)Cl)_2$	XPhos	K_2CO_3	1,4-Dioxane	58
18	**$(Pd(allyl)Cl)_2$**	**XPhos**	**K_2CO_3**	**DCE**	**85**

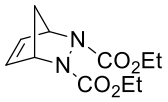
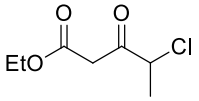
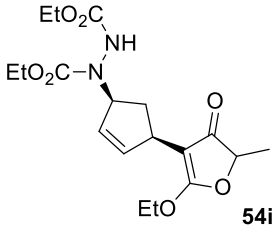
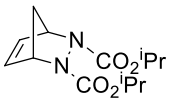
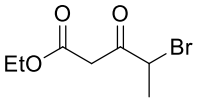
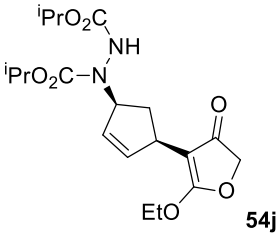
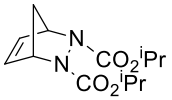
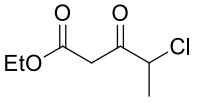
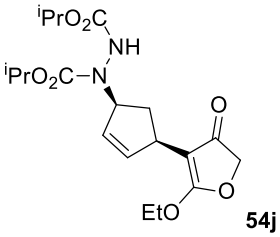
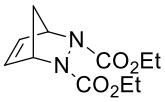
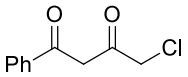
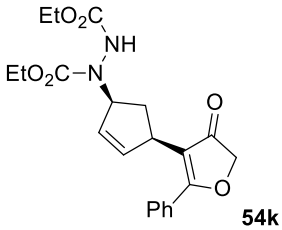
Reaction conditions: **4a** (1.0 equiv., 0.42 mmol), **53a** (1.5 equiv., 0.62 mmol), base (2.0 equiv.), catalyst (5 mol%), ligand (10 mol%), solvent (2.0 mL), 60 ^oC, 12 h, Isolated yields.

Under the optimised reaction conditions, the generality of the 3(2*H*)-furanone appended 3,5-disubstituted cyclopentene synthesis was studied with different diazabicyclic olefins and of 4-halo-1,3-dicarbonyl compounds (Table 4.2). The reactions of diazabicyclic adduct **4a** with ethyl-4-chloro acetoacetate **53a** and methyl-4-chloro acetoacetate **53b** afforded the corresponding products **54a** and **54b** in 85% and 88% yields respectively. In a similar way, the reactions of bicyclic adduct **4b** with **53a** and **53b** furnished the products **54c** and **54d** in excellent yields. There was a decrease in yield for 3(2*H*)-furanone appended hydrazino cyclopentenes **54e** (57%), **54f** (64%), **54g** (64%) and **54h** (75%) synthesized from bicyclic adducts **4c** and **4d**. The Pd-catalyzed reactions of ethyl 4-bromo-3-oxopentanoate **53c** with bicyclic adducts **4a** and **4b** were found to afford the products **54i** and **54j** in satisfactory yields whereas the use of 4-chloro-3-oxopentanoate **53d** instead of **53c** resulted in better reactions affording **54i** and **54j** in good to excellent yields. A phenyl moiety was introduced to the 5th position of 3(2*H*)-furanone moiety of **54k** by starting from 4-chloro-1-phenylbutane-1,3-dione **53e** and bicyclic adduct **4a**. In all cases the product was isolated as racemic mixture.

Table 4.2. Generality of 3(2*H*)-furanone appended hydrazino cyclopentene synthesis from diazabicyclic olefins and of 4-halo-1,3-dicarbonyl compounds

Entry	Bicyclic olefin	4-Halo-1,3-dicarbonyl compounds	Product	Yield (%)
1	 **4a**	 **53a**	 **54a**	85
2	 **4a**	 **53b**	 **54b**	88

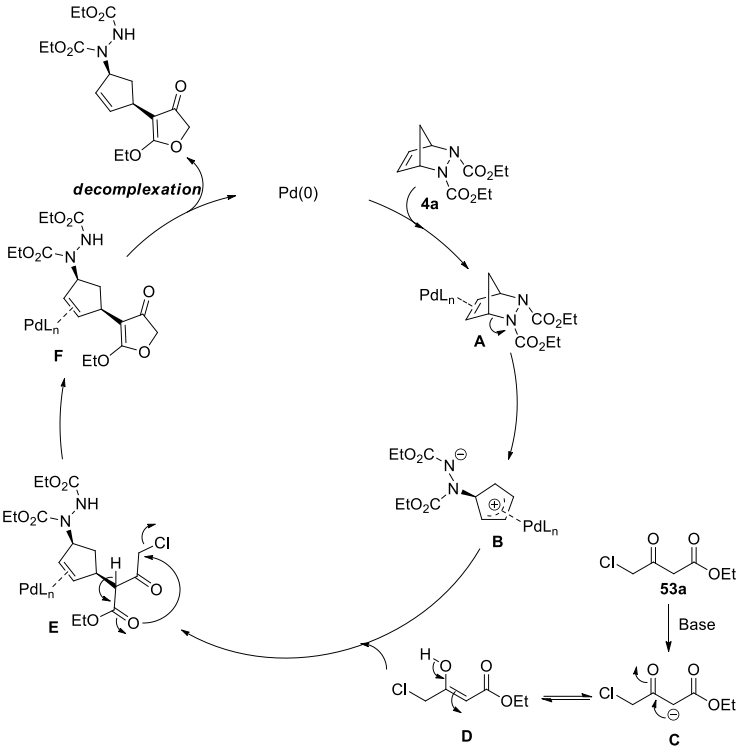
3	 **4b**	 **53a**	 **54c**	82
4	 **4b**	 **53b**	 **54d**	87
5	 **4c**	 **53a**	 **54e**	57
6	 **4c**	 **53b**	 **54f**	64
7	 **4d**	 **53a**	 **54g**	64
8	 **4d**	 **53b**	 **54h**	75
9	 **4a**	 **53c**	 **54i**	46

10	 **4a**	 **53d**	 **54i**	82
11	 **4b**	 **53c**	 **54j**	55
12	 **4b**	 **53d**	 **54j**	72
13[a]	 **4a**	 **53e**	 **54k**	35

Reaction conditions: **4** (1.0 equiv., 1.05 mmol), **53** (1.5 equiv., 1.58 mmol), K_2CO_3 (2.0 equiv.), $(Pd(allyl)Cl)_2$ (5 mol%), XPhos (10 mol%), DCE (5.0 mL), 60 °C, 12 h, Isolated yields. [a]: rt.

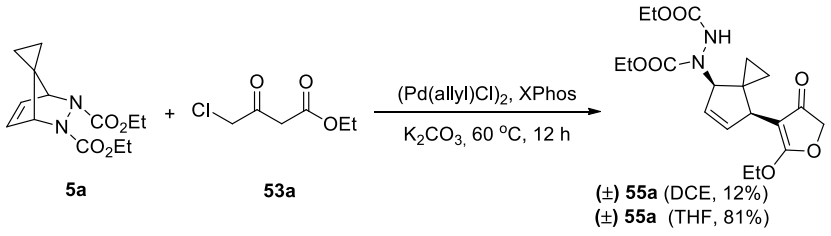
We propose a mechanism (scheme 4.27) for the Pd-catalyzed synthesis of 3(2*H*)-furanone appended hydrazino cyclopentene from diazabicyclic olefin and 4-halo acetoacetate based on literature precedents.[23-26] The reaction proceeds through three stages; the first one being the attack of Pd(0) species to the double bond (through *exo*-face) of the diazabicyclic olefin **1a** to form the π-allylpalladium intermediate **B** by the cleavage of one C-N bond (*endo* phase). The second stage involves the attack of the anionic species **C** or **D** (generated from **53a**) to one end of the π-allylpalladium intermediate (through the opposite side of that of Pd) **B** generating the species **E**. A base induced intramolecular cyclization occurs in the 4-haloacetoacetate part in **E** forming the intermediate **F** with a 3(2*H*)-furanone moiety appended. Alternatively, the furanone ring formation can take place *via* the oxidative addition of Pd(0)Ln to the C–Cl bond of **E** followed by conversion to oxy-π-allylpalladium intermediate and subsequent ring-closing (chapter 1, scheme 1.39). In the final stage decomplexation of the catalytic species occurs

releasing the product and Pd(0) to continue the catalytic cycle. The classical double inversion mechanism is the reason for the *cis*-stereochemistry in the product.



Scheme 4.27

Having established a methodology for accessing 3(2*H*)-furanone appended hydrazino cyclopentene from diazabicyclic olefins and 4-halo-1,3-dicarbonyl compounds, we were interested in expanding the scope of the olefins used. In this line, we checked the reactivity of spirotricyclic olefin **5a** with ethyl-4-chloro acetoacetate **53a** under the optimized conditions developed for diazabicyclic olefin. As expected the 3(2*H*)-furanone substituted hydrazino-spiro[2.4]hept-5-ene **55a** was isolated from the reaction in 12% yield (Scheme 4.28). A significant improvement in the yield of **55a** to 81% was observed when the solvent was changed from DCE to THF.



Scheme 4.28.

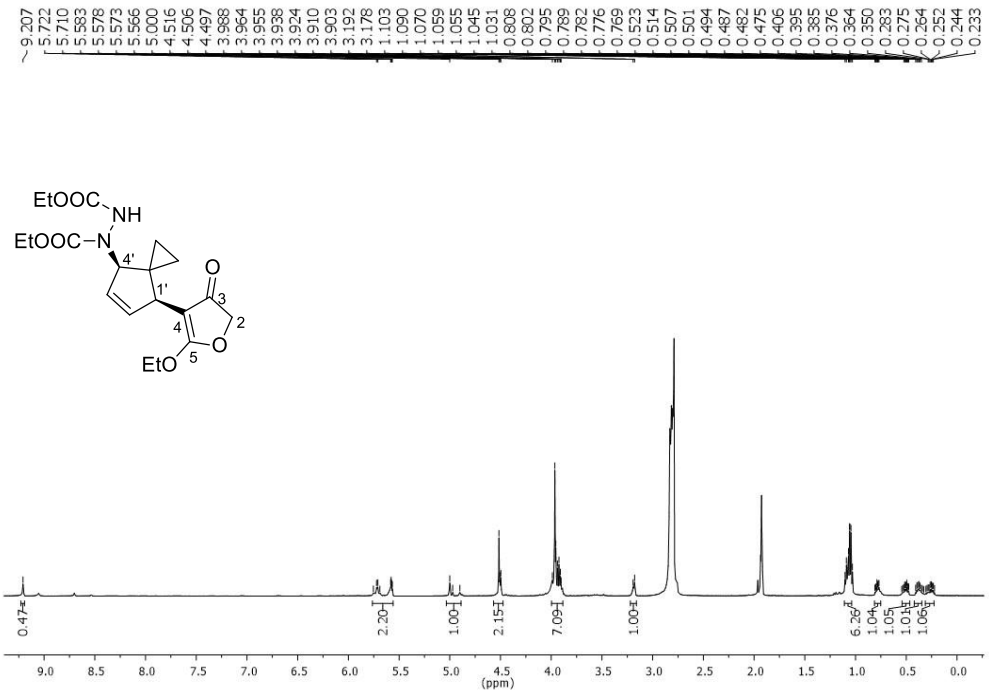


Figure 4.6. ^{1}H NMR spectrum of compound **55a**.

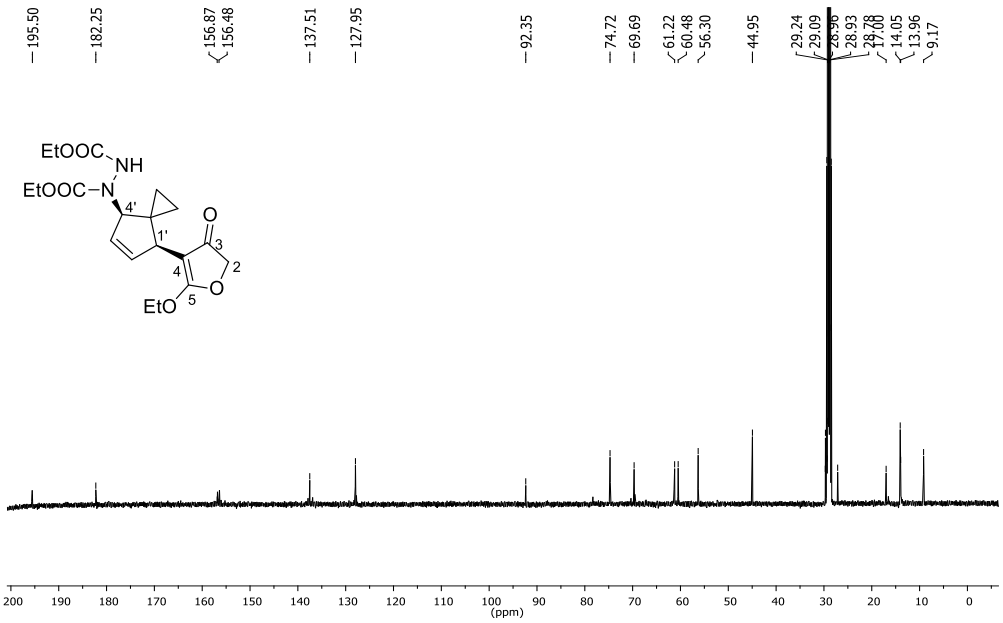


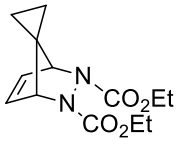
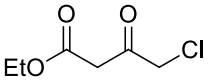
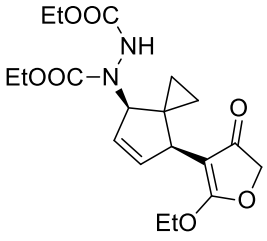
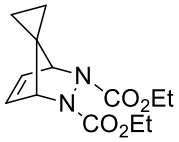
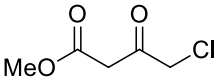
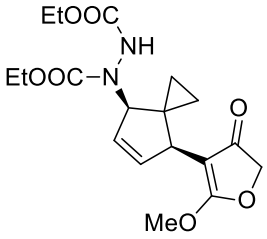
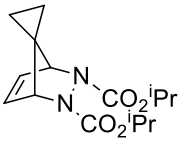
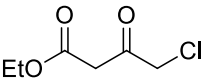
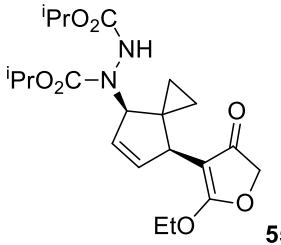
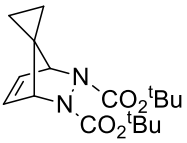
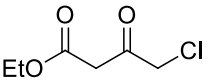
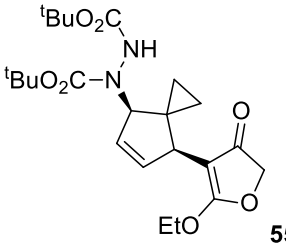
Figure 4.7. ^{13}C NMR of compound **55a**.

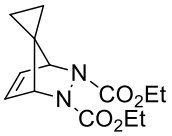
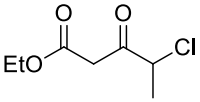
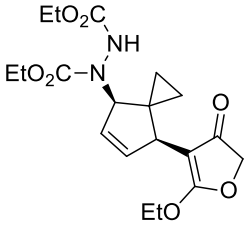
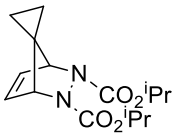
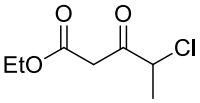
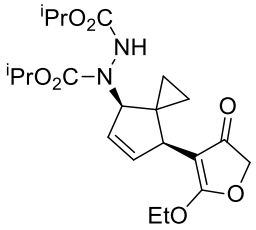
The structure of **55a** was assigned based on ^{1}H NMR, ^{13}C NMR, 2-D NMR and high-resolution mass spectral analyses. In the ^{1}H NMR spectrum (Fig. 4.6) the characteristic spiro protons resonated in the range 0.23-0.81 ppm. The alkene protons resonated in between 5.57-5.72 ppm and the proton attached to the carbon bearing hydrazine moiety resonated at 5.00 ppm. The C2 methylene protons resonated at 4.51 ppm. In the ^{13}C NMR spectrum (Fig. 4.7) the spiro carbon resonated at 9.2 ppm and the furanone carbonyl resonated at 195.5 ppm. The

ester carbonyls on the hydrazine moiety resonated at 156.9 and 156.5 ppm respectively. The alkene carbons resonated at 137.5 and 127.9 ppm respectively. The C2 carbon in the furanone ring resonated at 74.7 ppm. All other signals in the ^{1}H and ^{13}C NMR spectra were in agreement with the proposed structure. The high resolution mass spectral analysis showed a peak at *m/z* 417.1639 $(M+Na)^{+}$, which also supported the proposed structure.

The generality of the Pd-catalyzed ring opening of spirotricyclic olefins with 4-halo-1,3-dicarbonyl compounds were then investigated (Table 4.3). In all cases the product was isolated as racemic mixture.

Table 4.3. Generality of 3(2*H*)-furanone substituted hydrazino-spiro[2.4]hept-5-enesynthesis from diazabicyclic olefins and of 4-halo-1,3-dicarbonyl compounds

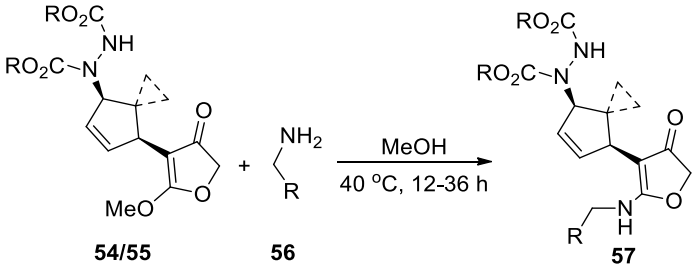
Entry	Spirotricyclic olefin	4-Halo-1,3-dicarbonyl compounds	Product	Yield (%)
1	 **5a**	 **53a**	 **55a**	81
2	 **5a**	 **53b**	 **55b**	76
3	 **5b**	 **53a**	 **55c**	75
4	 **5c**	 **53a**	 **55d**	87

5	 **5a**	 **53d**	 **55e**	52
6	 **5b**	 **53d**	 **55f**	45

Reaction conditions: **5** (1.0 equiv., 1.05 mmol), **53** (1.5 equiv., 1.58 mmol), K_2CO_3 (2.0 equiv.), $(Pd(allyl)Cl)_2$ (5 mol%), XPhos (10 mol%), THF (5.0 mL), 60 °C, 12 h, Isolated yields.

The reactions of the olefins **5a-c** with 4-chloro-ethyl/methyl acetoacetates **53a-b** afforded the corresponding 3(2*H*)-furanone substituted hydrazino-spiro[2.4]hept-5-enes **55a-d** in good to excellent yields. The reactions of 4-chloro-3-oxopentanoate **53d** with spirotricyclic olefins **5a** & **5b** also afforded the expected products **55e** and **55f** in 52% and 45% yields respectively.

Our next attempt was to utilize the synthesized 3(2*H*)-furanone appended hydrazino cyclopentenes for the generation of biologically relevant azaprostaglandin analogues.[27] This transformation was effected by treating the 3(2*H*)-furanone appended hydrazino cyclopentene with an amine in MeOH at 40 °C. The nucleophilic substitution of amine over the C5 position of furanone afforded the azaprostaglandin analogues (Scheme 4.29).



54/55 **56** **57**

Scheme 4.29

The reaction of **54h** with hexylamine **56a** was carried out first and the reaction afforded the corresponding the azaprostaglandin analogue in 98% yield. The structure of the product was confirmed using ^{1}H NMR, ^{13}C NMR and high-resolution mass spectral analyses. In the ^{1}H NMR spectrum (Fig. 4.8) the methylene protons adjacent to the nitrogen atom resonated as a multiplet at 3.22-3.30 ppm. The other protons in the hexyl chain resonated at 1.54, 1.44-1.27

and 0.90-0.88 ppm respectively. In the ^{13}C NMR (Fig. 4.9) the methylene carbon adjacent to the nitrogen atom was resonated at 41.5 ppm. The furanone carbonyl and C2 methylene carbons resonated at 191.4 and 74.1 ppm respectively. All other signals in the ^{1}H and ^{13}C NMR spectra were in agreement with the proposed structure. The high resolution mass spectral analysis showed a peak at *m/z* 570.2579 $(M+Na)^{+}$, which also supported the proposed structure.

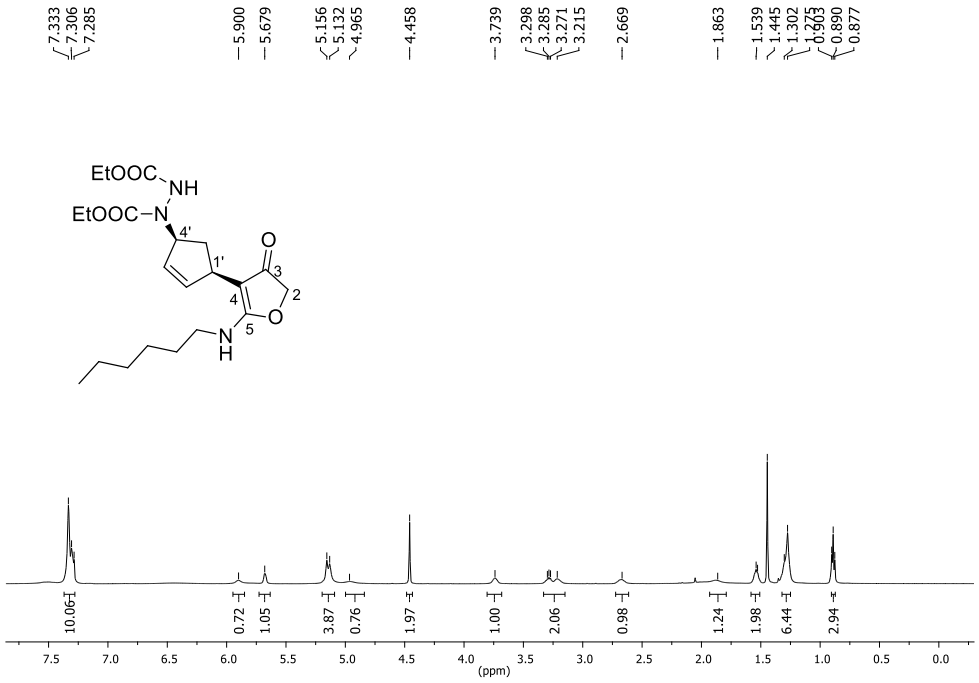


Figure 4.8. ^{1}H NMR spectrum of compound **57a.**

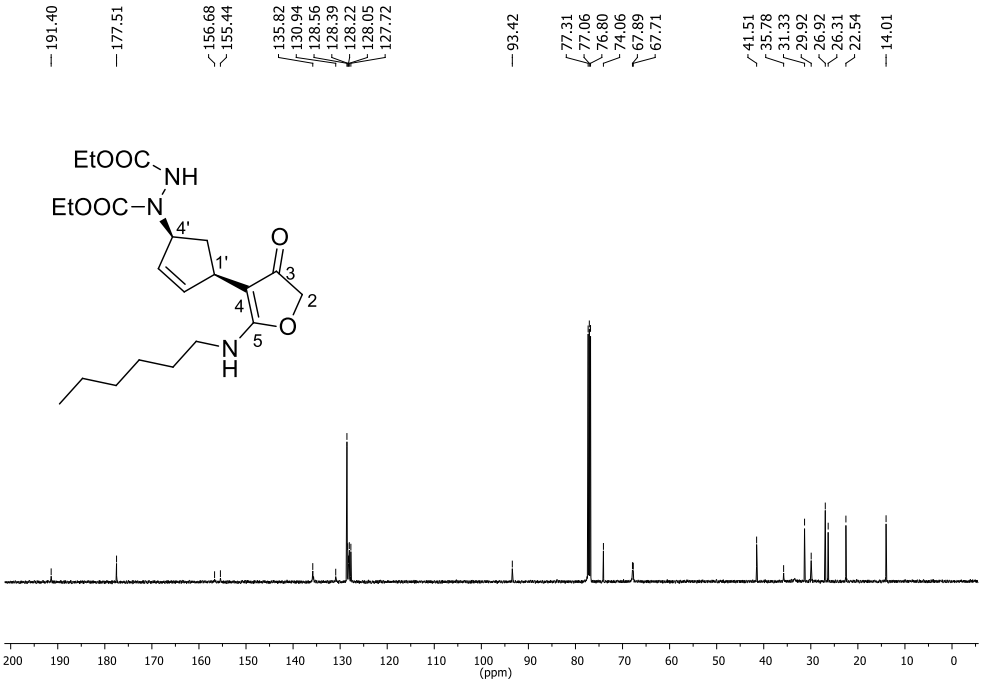
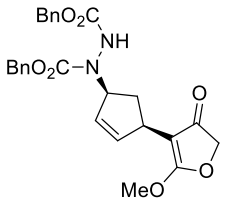
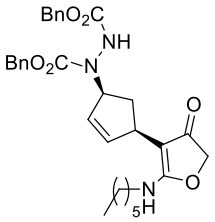
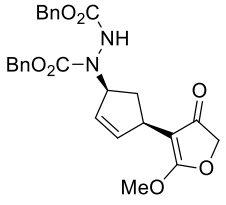
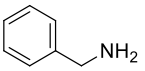
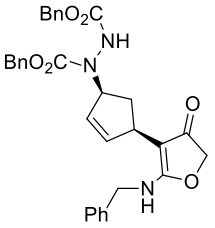
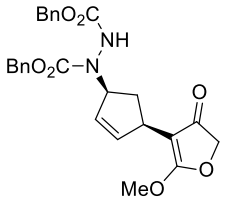
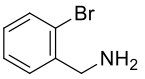
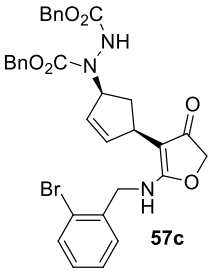
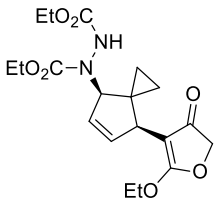
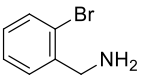
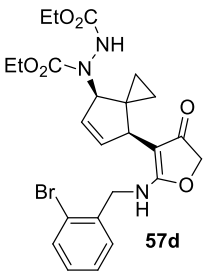
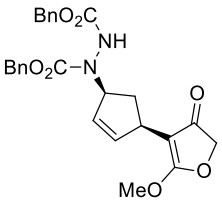
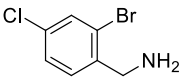
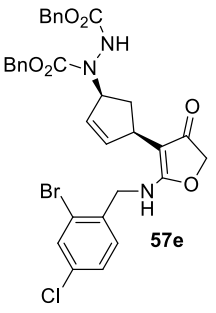
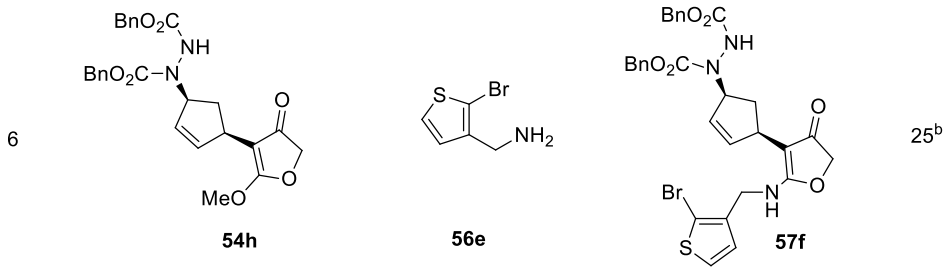


Figure 4.9. ^{13}C NMR spectrum of compound **57a.**

Different heterocyclic analogues of prostaglandins were made with different substituted amines. These reactions were found to be completed in 12 to 24 h from which the respective azaprostaglandin analogues **57a-f** were isolated in moderate to excellent yields (Table 4.4).

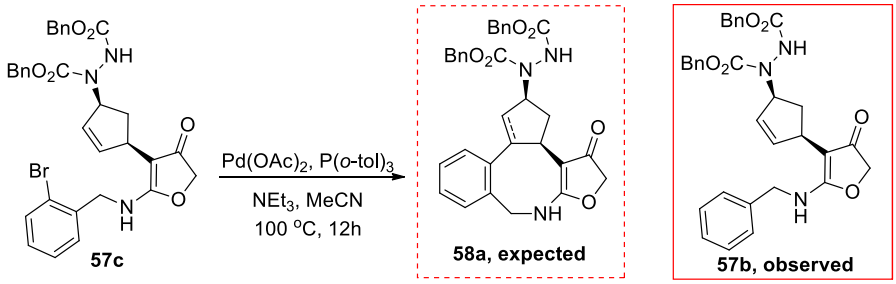
Table 4.4. Generality of azaprostaglandin synthesis from 3(2*H*)-furanone appended hydrazino cyclopentenes[a]

Entry	3(2*H*)-furanone appended hydrazino cyclopentene	Amine	Product	Yield (%)
1	 **54h**	 **56a**	 **57a**	98[a]
2	 **54h**	 **56b**	 **57b**	92[a]
3	 **54h**	 **56c**	 **57c**	72[a]
4	 **55a**	 **56c**	 **57d**	50[b]
5	 **54h**	 **56d**	 **57e**	37[b]



Reaction conditions: [a]**54/55** (1.0 equiv.), **56** (1.1 equiv.), MeOH (0.2 mM), 40 °C, 12 h, Isolated yields; [b] 24 h.

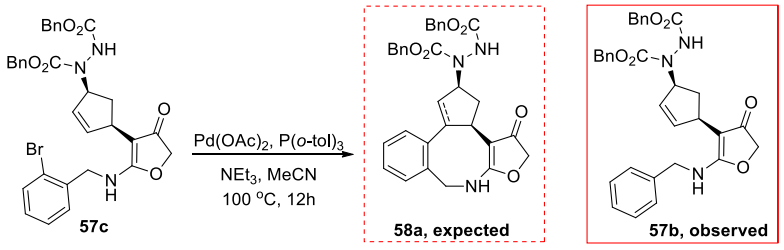
During the synthesis of azaprostaglandin analogues, we chose different *ortho*-bromo-benzylamines to access scaffolds that can be subjected to further transformations towards complex fused moieties. We hypothesized that, by subjecting compound **57c** to intramolecular Heck coupling conditions a tri-ring fused azocine moiety namely 3(2*H*)-furanone fused cyclopetano-benzoazocine could be synthesized.[28] The first trial run of the intramolecular Heck coupling of **57c** was carried out with $Pd(OAc)_2$ as the catalyst, P(*o*-tol)$_3$ as the ligand, Et_3N as the base in CH_3CN at 100 °C (Scheme 4.29). After 12 h, instead of the expected 3(2*H*)-furanone fused tetrahydroazocine **58a**, we isolated the dehalogenated product **57b**.



Scheme 4.29

We then tried different conditions by changing the Pd-catalyst, ligand, base and solvent to see if the expected 3(2*H*)-furanone fused cyclopetano-benzoazocine could be synthesized. All the attempts were in vain furnishing the dehalogenated product.

Table 4.5. Optimization studies[a]



Entry	Catalyst	Ligand	Base	Additives	Solvent	Yield of 57b (%)
1	$Pd(OAc)_2$	P(*o*-tol)$_3$	NEt_3	-	MeCN	62
2	$Pd(OCOCF_3)_2$	P(*o*-tol)$_3$	NEt_3	-	MeCN	52
3	$Pd(PPh_3)_4$	P(*o*-tol)$_3$	NEt_3	-	MeCN	trace
4	$PdCl_2$	P(*o*-tol)$_3$	NEt_3	-	MeCN	trace
5	$PdCl_2(PPh_3)_2$	P(*o*-tol)$_3$	NEt_3	-	MeCN	NR
6	$Pd(OAc)_2$	PPh_3	NEt_3	-	MeCN	50
7	Pd(OAc)2	*R*-BINAP	NEt_3	-	MeCN	50
8	$Pd(OAc)_2$	P(*o*-tol)$_3$	K_2CO_3	-	MeCN	NR
9	$Pd(OAc)_2$	P(*o*-tol)$_3$	DIEA	-	MeCN	trace
10	$Pd(OAc)_2$	P(*o*-tol)$_3$	NEt_3	-	Toluene	trace
11	$Pd(OAc)_2$	P(*o*-tol)$_3$	NEt_3	-	DMF	trace
12[b]	$Pd(OAc)_2$	P(*o*-tol)$_3$	NEt_3	-	MeCN	65
13	$Pd(OAc)_2$	-	DIEA	-	NMP	NR
14	$Pd(OAc)_2$	*R*-BINAP	TMEDA	HCOOH	MeCN	NR
15	$Pd(OAc)_2$	P(*o*-tol)$_3$	-	HCOONa	MeCN	trace

16	$Pd(OAc)_2$	P(*o*-tol)$_3$	NEt_3	HCOONa	MeCN	trace
17	$Pd(OAc)_2$	P(*o*-tol)$_3$	NEt_3	HCOONa/ TBAB	MeCN	NR
18	$Pd(OAc)_2$	P(*o*-tol)$_3$	NEt_3	Bu_4NCl	MeCN	trace

Reaction conditions: [a] **57c** (1.0 equiv., 0.05 mmol), base (1.0 equiv.), catalyst (10 mol%), ligand (10 mol%), additives (1.0 equiv.), solvent (2.0 mL), 12 h, 100 °C, Isolated yields are reported; [b] catalyst (5 mol%).

The reason for failure might be due to the fact that oxidatively added palladium species might be not in a bonding distance with that of the alkene (of cyclopentene) for insertion reaction.

4.6 Conclusion

We have developed a methodology for the desymmetrization of diazabicyclic olefins *via* a Pd-catalyzed reaction with 4-halo-1,3-dicarbonyl compounds. This reaction has resulted in the generation of a new class of 3(2*H*)-furanone appended hydrazino cyclopentenes. This ring opening reaction of diazabicyclic olefins was found to be general with different 4-halo-1,3-dicarbonyl compounds and we could also synthesize another interesting scaffold namely, 3(2*H*)-furanone substituted spiro[2.4]hept-5-ene from cyclopropane-appended spirotricyclic olefin. We have proposed a mechanism which proceeds *via* the formation of a π-allylpalladium intermediate which is quenched by the active methylene moiety generated from 4-halo1,3-dicarbonyl moiety and an intramolecular cyclization in the intermediate generating the product. We then utilized the synthesized 3(2*H*)-furanone appended hydrazino cyclopentenes for the generation of azaprostaglandin analogues. Finally, we tried to generate a new family of 3(2*H*)-furanone fused tetrahydroazocine derivatives from appropriately functionalized azaprostaglandin analogues which did not result in the expected outcome.

4.7 Experimental section

4.7.1 General experimental methods

All chemicals were of the best grade commercially available and were used without further purification. All solvents were purified according to the standard procedures; dry solvents were obtained according to the literature methods and stored over molecular sieves. Analytical thin-layer chromatography was performed on polyester sheets precoated with silica gel containing

fluorescent indicator (POLYGRAMSIL G/ UV254). Gravity column chromatography was performed using silica, and mixtures of ethyl acetate hexanes were used for elution. Melting points were measured with a Fisher John melting point apparatus and are uncorrected. NMR spectra were recorded with Bruker Avance-500 (500 MHz for ^{1}H NMR, 125 MHz for ^{13}C NMR) spectrophotometer instruments. All spectra were measured at 300 K, unless otherwise specified. The chemical shifts δ are given in ppm and referenced to the external standard TMS or internal solvent standard. ^{1}H NMR coupling constants (*J*) are reported in Hertz (Hz) and multiplicities are indicated as follows s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublets). Mass spectra were performed with a Thermo Finnigan MAT95XL, a Thermo Fisher Scientific LTQ Orbitrap Velos, and an Agilent 6890 gas chromatograph with JMS-T100GC spectrometer or with a ESI/HRMS at 60,000 resolution using Thermo Scientific Exactive mass spectrometer with orbitrap analyzer.

All chemicals were purchased from TCI Chemicals, Sigma-Aldrich or Spectrochem. 4-Bromoacetoacetates and 4-Chlorooacetoacetates were prepared by the reported procedures.

The synthesized 3(2*H*)-furanone-appended cyclopentenes contains hydrazide moieties, and the peaks in ^{1}H and ^{13}C NMR spectra were broadened (or doubled) by the presence of amide rotamers.[29]

4.7.2 Experimental procedure for the synthesis starting materials

4.7.2A Experimental procedure for the synthesis of diazabicyclic olefin (4a-d): To a stirred solution of dialkyldizodicarboxylate (1.0 equiv.) (ethyl, isopropyl, *tert*-butyl, benzyl) in diethylether at 0 ^{o}C, cyclopentadiene (2.0 equiv) was added dropwise and continued stirring for another 12h at room temperature. The solvent was evaporated *in vacuo* and the residue on silica gel (100–200 mesh) column chromatography using mixtures of hexanes/ethyl acetate as eluents, affording the corresponding diazabicyclic olefin.

4.7.2B Experimental procedure for the synthesis of spirotricyclic olefin (5a-c): Under argon atmosphere cyclopentadiene (1.0 equiv.) was added to an ice cooled solution of KOH (2.75 equiv.) and triethylbenzylammonium chloride (0.01 equiv.) in DCM. To this 1,2-dichloroethane (1.0 eqiv.) was added and allowed to stir for 12 h at room temperature. When the reaction was completed, the reaction mixture was filtered and to the ice cooled filtrate dialkyldizodicarboxylate (1.2 equiv.) was added and continue stirring for another 12 h at room temperature. The solvent was evaporated *in vacuo* and the residue on silica gel (100–200 mesh)

column chromatography using mixtures of hexanes/ethyl acetate as eluents, affording the corresponding spirotricyclic olefin.

4.7.2C Experimental procedure for the synthesis of 4-halo-1,3-dicarbonyl compounds (53d-e)

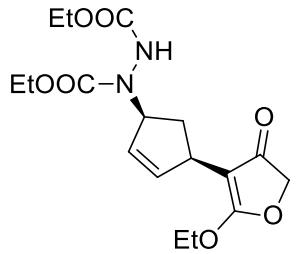
Under nitrogen atmosphere, to a stirred solution of 1,3-dicarbonyl compounds (1.0 equiv.) (methyl-3-oxopentanoate, benzoylacetone) in DCM (0.2 mM), add benzyltrimethylammonium chloride (2.0 equiv.) and the mixture was stirred at room temperature for 24 h. After the completion of reaction as indicated by TLC, sodium thiosulphate solution was added and stirred for another 10 min. The combined organic layers were dried over sodium sulphate and the solvent was evaporated *in vacuo.* The residue on silica gel (100–200 mesh) column chromatography using mixtures of hexanes/ethyl acetate as eluents (1% EtOAc in Hexane), affording the 4-chloro-1,3-dicarbonyl compounds **53d-e**.

4.7.3 Experimental procedure for the synthesis of 3(2*H*)-furanone appended hydrazino cyclopentene: A mixture of diazabicyclic olefin (1.0 equiv.), 4-haloacetoacetate (1.5 equiv.), $[Pd(allylCl)]_2$ (5 mol%), Xphos (10 mol%) and K_2CO_3 (2.0 equiv.) was weighed into a dry Schlenk tube and degassed for 10 minutes. Anhydrous DCE (0.2 mM) was added and the reaction mixture was purged with argon and allowed to stir at 60 ^oC for 12 h. The solvent was evaporated *in vacuo* and the residue on silica gel (100–200 mesh) column chromatography using mixtures of hexanes/ethyl acetate as eluents, affording the corresponding 3(2*H*)-furanone appended hydrazino cyclopentene.

Synthesis and characterization of 3(2*H*)-furanone appended hydrazino cyclopentenes 54a-k

Diethyl-1-((1*S*,4*R*)-4-(2-ethoxy-4-oxo-4,5-dihydrofuran-3-yl)cyclopent-2-en-1-yl)hydrazine-1,2-dicarboxylate (54a) : The reaction was performed according to the general procedure with diazabicyclic olefin (derived from cyclopentadiene and diethylazadicarboxylate) **4a** (100 mg, 0.42 mmol), ethyl-4-chloroacetoacetate **53a** (103 mg, 0.62 mmol), $[Pd(allyl)Cl]_2$ (8 mg, 0.02 mmol), Xphos (20 mg, 0.04 mmol) and K_2CO_3 (115 mg, 0.83 mmol) in dry DCE was stirred at 60 ^oC for 12h. Upon completion of the reaction as indicated by TLC, the solvent was removed and the crude product was purified over silica gel (100-200 mesh) column chromatography (70% ethyl acetate in hexanes) to afford the product **54a** as pale-yellow viscous liquid (130 mg, 85%)

Analytical data of 54a



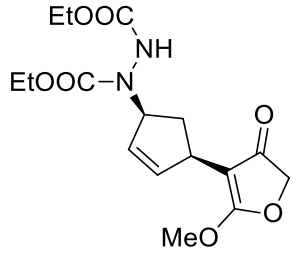
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 5.65-5.57 (m, 2H), 5.32 (brs, 1H), 4.46 (s, 2H), 4.42-4.38 (m 2H), 4.11 (brs, 5H), 3.42-3.40 (m, 1H), 2.51 (brs, 1H), 1.84 (brs, 1H), 1.37 (t, *J* = 7.0 Hz, 3H), 1.21-1.16 (m, 6H) ppm.

^{13}C NMR (125 MHz, CDCl3): δ 195.8, 181.2, 156.8, 156.1, 136.6, 129.0, 128.4, 95.2, 74.7, 66.2, 62.2, 61.5, 36.4, 32.8, 14.7, 14.5 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$ calcd for $C_{17}H_{24}N_2NaO_7$: 391.1476; Found: 391.1486

Diethyl-1-((1*S*,4*R*)-4-(2-methoxy-4-oxo-4,5-dihydrofuran-3-yl)cyclopent-2-en-1-yl)hydrazine-1,2-dicarboxylate (54b): Following the general experimental procedure, Diazabicyclic olefin **4a** (100 mg, 0.4162 mmol), methyl-4-chloroacetoacetate **53b** (94 mg, 0.62 mmol), $[Pd(allyl)Cl]_2$ (8 mg, 0.02 mmol), X-phos (20 mg, 0.04 mmol) and K_2CO_3 (115 mg, 0.83 mmol) in dry DCE was stirred at 60 ^oC for 12h. The crude product was purified over silica gel (100-200 mesh) column chromatography (70% ethyl acetate in hexanes) to afford the desired product **54b** as pale-yellow viscous liquid (131 mg, 89%).

Analytical data of 54b



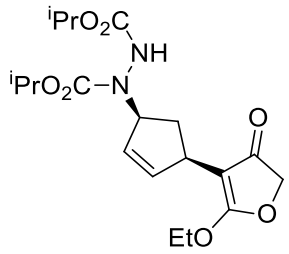
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 5.64- 5.58 (m, 2H), 5.31 (brs, 1H), 4.48 (s, 2H), 4.11 (brs, 5H), 4.00 (s, 3H), 3.42-3.38 (m, 1H), 2.51 (brs, 1H), 1.82-1.80 (m, 1H), 1.20-1.16 (m, 6H) ppm

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 195.8, 181.4, 156.8, 156.0, 136.5, 128.9, 128.5, 95.3, 74.8, 66.6, 64.1, 62.1, 61.5, 56.4, 36.2, 32.7, 14.5 ppm

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$ calcd for $C_{16}H_{22}N_2NaO_7$: 377.1319; Found: 377.1364

Diisopropyl-1-((1*S*,4*R*)-4-(2-ethoxy-4-oxo-4,5-dihydrofuran-3-yl)cyclopent-2-en-1-yl)hydrazine-1,2-dicarboxylate (54c): Following the general experimental procedure, Diazabicyclic olefin **4b** (100 mg, 0.37 mmol), ethyl-4-chloroacetoacetate **53a** (92 mg, 0.56 mmol), $[Pd(allyl)Cl]_2$ (7 mg, 0.02 mmol), X-phos (18 mg, 0.04 mmol) and K_2CO_3 (103 mg,

0.75 mmol) in dry DCE was stirred at 60 60 °C for 12h. The crude product was purified over silica gel (100-200 mesh) column chromatography (70% ethyl acetate in hexanes) to afford the desired product **54c** as yellow viscous liquid (122 mg, 82%)



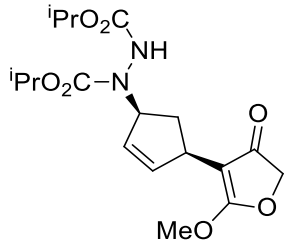
Analytical data of 54c

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 5.66- 5.58 (m, 2H), 5.33 (brs, 1H), 4.93-4.85 (m, 2H), 4.47-4.37 (m, 5H), 3.42-3.40 (m, 1H), 2.49-2.47 (m, 1H), 1.93 (brs, 1H), 1.36 (t, *J* = 7.0 Hz, 3H), 1.19-1.17 (m, 12H) ppm

^{13}C NMR (125 MHz, $CDCl_3$): δ 195.7, 181.2, 156.3, 155.6, 136.9, 136.3, 129.2, 128.6, 95.2, 74.6, 69.5, 69.0, 66.3, 66.1, 63.8, 36.2, 29.2, 22.1, 22.0, 14.8 ppm

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$ calcd for $C_{19}H_{28}N_2NaO_7$ 419.1789; Found: 419.1782

Diisopropyl-1-((1*S*,4*R*)-4-(2-methoxy-4-oxo-4,5-dihydrofuran-3-yl)cyclopent-2-en-1-yl)hydrazine-1,2-dicarboxylate (54d): Following the general experimental procedure, Diazabicyclic olefin **4b** (100 mg, 0.37 mmol), methyl-4-chloroacetoacetate **53b** (84 mg, 0.56 mmol), $[Pd(allyl)Cl]_2$ (7 mg, 0.02 mmol), X-phos (18 mg, 0.04 mmol) and K_2CO_3 (103 mg, 0.75 mmol) in dry DCE was stirred at 60 °C for 12h The crude product was purified over silica gel (100-200 mesh) column chromatography (70% ethyl acetate in hexanes) to afford the desired product **54d** as yellow viscous liquid (130 mg, 87%).



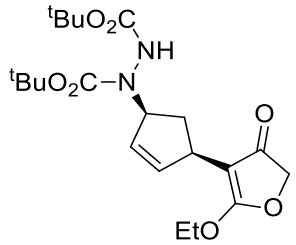
Analytical data of 54d

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 5.65- 5.58 (m, 2H), 5.32 (brs, 1H), 4.86-4.85 (m, 2H), 4.48 (s, 2H), 3.99 (s, 3H), 3.41 (brs, 1H), 2.46 (brs, 1H), 1.80 (brs, 1H), 1.18-1.17 (m, 12H) ppm

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 195.6, 181.4, 156.3, 155.6, 155.5, 136.1, 129.2, 128.7, 95.9, 95.2, 74.7, 69.5, 69.1, 63.7, 56.5, 56.3, 36.1, 35.9, 32.7, 32.1, 22.1, 21.9 ppm

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$ calcd for $C_{18}H_{26}N_2NaO_7$: 405.1632; Found: 405.1640

Di-*tert*-butyl 1-((1*S*,4*R*)-4-(2-ethoxy-4-oxo-4,5-dihydrofuran-3-yl)cyclopent-2-en-1-yl)hydrazine-1,2-dicarboxylate (54e): Following the general experimental procedure, Diazabicyclic olefin **4c** (100 mg, 0.34 mmol), ethyl-4-chloroacetoacetate **53a** (83 mg, 0.51 mmol), $[Pd(allyl)Cl]_2$ (6 mg, 0.02 mmol), X-phos (16 mg, 0.03 mmol) and K_2CO_3 (93 mg, 0.68 mmol) in dry DCE was stirred at 60 ^oC for 12h The crude product was purified over silica gel (100-200 mesh) column chromatography (40% ethyl acetate in hexanes) to afford the desired product **54e** as yellow viscous liquid (82 mg, 57%).



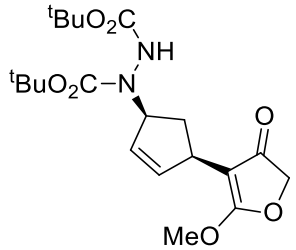
Analytical data of 54e

^1H NMR (500 MHz, $CDCl_3$, TMS): δ 5.66-5.61 (m, 2H), 5.29-5.14 (m, 1H), 4.52-4.37 (m, 5H), 3.40 (m, 1H), 2.44 (s, 1H), 1.78 (brs, 3H), 1.38-1.37 (m, 18H) ppm

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 195.7, 181.3, 155.1, 154.8, 135.4, 129.7, 95.4, 80.6, 74.7, 66.0, 36.1, 31.9, 28.2, 28.0, 14.6 ppm

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$ calcd for $C_{21}H_{32}N_2NaO_7$: 447.2102; Found: 447.2089.

Di-*tert*-butyl 1-((1*S*,4*R*)-4-(2-methoxy-4-oxo-4,5-dihydrofuran-3-yl)cyclopent-2-en-1-yl)hydrazine-1,2-dicarboxylate (54f): Following the general experimental procedure, Diazabicyclic olefin **4c** (100 mg, 0.34 mmol), methyl-4-chloroacetoacetate **53b** (76 mg, 0.51 mmol), $[Pd(allyl)Cl]_2$ (6 mg, 0.02 mmol), X-phos (16 mg, 0.03 mmol) and K_2CO_3 (93 mg, 0.68 mmol) in dry DCE was stirred at 60 60 ^oC for 12h. The crude product was purified over silica gel (100-200 mesh) column chromatography (40% ethyl acetate in hexanes) to afford the desired product **54f** as yellow viscous liquid (89 mg, 64%).



Analytical data of 54f

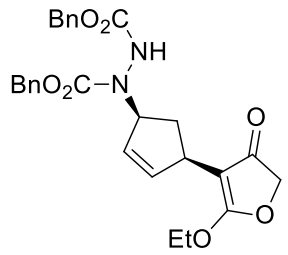
^1H NMR (500 MHz, $CDCl_3$, TMS): δ 5.72 (brs, 2H), 5.36 (brs, 1H), 4.54 (s, 2H), 4.01 (s, 3H), 3.48 (s, 1H), 2.52 (brs, 1H), 1.90-1.84 (m, 1H), 1.47-1.46 (m, 18H) ppm

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 195.7, 181.3, 155.5, 155.0, 135.7, 129.7, 95.7, 81.0, 80.6, 74.7, 56.4, 56.2, 36.1, 33.1, 32.0, 29.7, 28.3 ppm

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$ calcd for $C_{20}H_{30}N_2NaO_7$: 433.1945; Found: 433.1961

Dibenzyl 1-((1*S*,4*R*)-4-(2-ethoxy-4-oxo-4,5-dihydrofuran-3-yl)cyclopent-2-en-1-yl)hydrazine-1,2-dicarboxylate (54g): Following the general experimental procedure, Diazabicyclic olefin **4d** (100 mg, 0.27 mmol), ethyl-4-chloroacetoacetate **53a** (68 mg, 0.41 mmol), $[Pd(allyl)Cl]_2$ (5 mg, 0.01 mmol), X-phos (13 mg, .03 mmol) and K_2CO_3 (76 mg, 0.55 mmol) in dry DCE was stirred at 60 60 ^oC for 12h The crude product was purified over silica gel (100-200 mesh) column chromatography (60% ethyl acetate in hexanes) to afford the desired product **54g** as brown viscous liquid (90 mg, 67%).

Analytical data of 54g



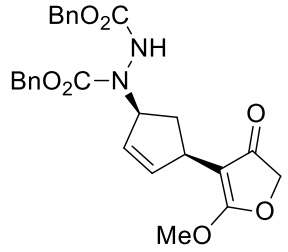
^1H NMR (500 MHz, $CDCl_3$, TMS): δ 7.24-7.19 (m, 10H), 5.62-5.32 (m, 3H), 5.08-4.99 (m, 4H), 4.48-4.36 (m, 4H), 3.39 (s, 1H), 2.51 (brs, 1H), 1.91 (brs, 1H), 1.35-1.32 (m, 3H) ppm

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 195.9, 181.3, 156.8, 156.5, 155.8, 137.1, 136.3, 128.7, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.6, 127.4, 95.0, 74.7, 67.5, 67.1, 66.8, 66.4, 64.3, 36.6, 32.3, 14.7 ppm

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$ calcd for $C_{27}H_{28}N_2NaO_7$: 515.1782; Found: 515.1789

Dibenzyl 1-((1*S*,4*R*)-4-(2-methoxy-4-oxo-4,5-dihydrofuran-3-yl)cyclopent-2-en-1-yl)hydrazine-1,2-dicarboxylate (54h): Following the general experimental procedure, Diazabicyclic olefin **4d** (100 mg, 0.27 mmol), methyl-4-chloroacetoacetate **53b** (62 mg, 0.41 mmol), $[Pd(allyl)Cl]_2$ (5 mg, 0.01 mmol), X-phos (13 mg, .03 mmol) and K_2CO_3 (76 mg, 0.55 mmol) in dry DCE was stirred at 60 60 ^oC for 12h The crude product was purified over silica gel (100-200 mesh) column chromatography (60% ethyl acetate in hexanes) to afford the desired product **53h** as brown viscous liquid (98 mg, 75%)

Analytical data of 58h



^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.26-7.22 (m, 10H), 5.63-5.40 (m, 3H), 5.10-5.01 (m, 4H), 4.52-4.41 (m, 2H), 3.98 (s, 3H), 3.40 (s, 1H), 2.52 (brs, 1H), 1.89 (brs, 1H) ppm

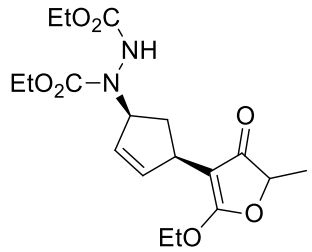
^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 195.8, 181.4, 156.7, 155.8, 136.9, 136.3, 128.8, 128.4, 128.4, 128.0, 127.9, 95.1, 74.8, 67.6, 67.1, 64.3, 56.3, 36.4, 32.3 ppm

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$ calcd for $C_{26}H_{26}N_2NaO_7$: 501.1632; Found: 501.1625

Diethyl 1-((1*S*,4*R*)-4-(2-ethoxy-5-methyl-4-oxo-4,5-dihydrofuran-3-yl)cyclopent-2-en-1-yl)hydrazine-1,2-dicarboxylate (54i): Following the general experimental procedure, Diazabicyclic olefin **4a** (100 mg, 0.42 mmol), ethyl-4-bromo-3-oxopentanoate **53c** (139 mg, 0.62 mmol), $[Pd(allyl)Cl]_2$ (8 mg, 0.02 mmol), X-phos (20 mg, 0.04 mmol) and K_2CO_3 (115 mg, 0.83 mmol) in dry DCE was stirred at 60 60 ^{o}C for 12h. The crude product was purified over silica gel (100-200 mesh) column chromatography (40% ethyl acetate in hexanes) to afford the desired product **54i** as yellow viscous liquid (73 mg, 46%)

Following the general experimental procedure, Diazabicyclic olefin **4a** (100 mg, 0.42 mmol), ethyl-4-chloro-3-oxopentanoate **53d** (112 mg, 0.62 mmol), $[Pd(allyl)Cl]_2$ (8 mg, 0.02 mmol), X-phos (20 mg, 0.04 mmol) and K_2CO_3 (115 mg, 0.83 mmol) in dry DCE was stirred at 60 ^{o}C for 12h. The crude product was purified over silica gel (100-200 mesh) column chromatography (40% ethyl acetate in hexanes) to afford the desired product **54i** as yellow viscous liquid (130 mg, 82%).

Analytical data of 54i



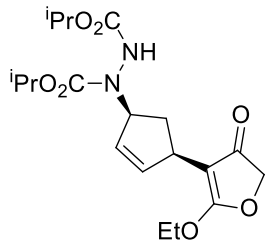
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 5.64-5.56 (m, 2H), 5.32 (brs, 1H), 4.57-4.54 (m, 1H), 4.38-4.36 (m, 2H), 4.14-4.11 (m, 4H), 3.41-3.39 (m, 1H), 2.50 (brs, 1H), 1.90 (m, 1H), 1.41-1.40 (m, 3H), 1.36 (t, *J* = 7.0 Hz , 3H), 1.18-1.15 (m, 6H) ppm

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 198.6, 180.0, 156.9, 156.1, 137.0, 128.8, 93.7, 82.9, 75.5, 66.1, 62.1, 36.5, 30.9, 29.7, 16.5, 14.7, 14.5 ppm

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$ calcd for $C_{18}H_{26}N_2NaO_7$: 405.1632; Found: 405.1629.

Diisopropyl 1-((1*S*,4*R*)-4-(2-ethoxy-5-methyl-4-oxo-4,5-dihydrofuran-3-yl)cyclopent-2-en-1-yl)hydrazine-1,2-dicarboxylate (54j): Following the general experimental procedure, Diazabicyclic olefin **4b** (100 mg, 0.37 mmol), ethyl-4-bromo-3-oxopentanoate **53c** (125 mg, 0.56 mmol), $[Pd(allyl)Cl]_2$ (7 mg, 0.02 mmol), X-phos (18 mg, 0.04 mmol) and K_2CO_3 (103 mg, 0.75 mmol) in dry DCE was stirred at 60 ^{O}C for 12h. The crude product was purified over silica gel (100-200 mesh) column chromatography (40% ethyl acetate in hexanes) to afford the desired product **54j** as yellow viscous liquid (85 mg, 55%)

Following the general experimental procedure, Diazabicyclic olefin **4b** (100 mg, 0.37mmol), ethyl-4-chloro-3-oxopentanoate **53d** (100 mg, 0.56 mmol), $[Pd(allyl)Cl]_2$ (7 mg, 0.02 mmol), X-phos (18 mg, 0.04 mmol) and K_2CO_3 (103 mg, 0.75 mmol) in dry DCE was stirred at 60 ^{o}C for 12h. The crude product was purified over silica gel (100-200 mesh) column chromatography (40% ethyl acetate in hexanes) to afford the desired product **54j** as yellow viscous liquid (115 mg, 75%).



Analytical data of 54j

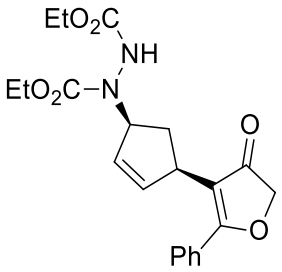
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 5.71-5.62 (m, 2H), 5.40 (brs, 1H), 4.96-4.91 (m, 2H), 4.58-4.57 (m, 1H), 4.44-4.42 (m, 2H), 3.46 (brs, 1H), 2.52 (brs, 1H), 1.97 (brs, 1H), 1.47-1.40 (m, 6H), 1.23 (brs, 12H) ppm

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 198.4, 179.9, 156.4, 155.7, 136.6, 129.0, 128.4, 93.5, 82.9, 69.5, 66.0, 36.5, 32.3, 22.1, 22.0, 16.6, 14.8 ppm

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$calcd for $C_{20}H_{30}N_2NaO_7$: 433.1945; Found: 433.1956.

Diethyl 1-((1*S*,4*R*)-4-(4-oxo-2-phenyl-4,5-dihydrofuran-3-yl)cyclopent-2-en-1-yl)hydrazine-1,2-dicarboxylate (54k): Following the general experimental procedure, Diazabicyclic olefin **4a** (100 mg, 0.42 mmol), 4-bromo-1-phenylbutane-1,3-dione **53e** (151 mg, 0.62 mmol), $[Pd(allyl)Cl]_2$ (8 mg, 0.02 mmol), X-phos (20 mg, 0.04 mmol) and K_2CO_3 (115 mg, 0.83 mmol) in dry DCE was stirred at rt for 12h. The crude product was purified over

silica gel (100-200 mesh) column chromatography (30% ethyl acetate in hexanes) to afford the desired product **54k** as pale-yellow viscous liquid (90 mg, 35%).



Analytical data of 54k

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.77-7.73 (m, 2H), 7.45 (brs, 1H), 7.43-7.20 (m, 2H), 5.99 (s, 1H), 5.79-5.73 (m, 2H), 4.22-4.17 (m, 2H), 4.11-4.10 (m, 5H), 3.15 (brs, 1H), 2.52 (brs, 1H), 1.94 (brs, 1H), 1.25-1.13 (m, 6H) ppm

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 203.3, 185.9, 155.8, 154.4,152.2, 132.8, 128., 127.1, 101.5, 87.3, 62.9,62.5, 62.0, 46.5, 30.9, 2.7, 14.5,14.1,14.1 ppm

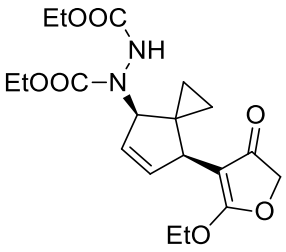
HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$calcd for $C_{21}H_{24}N_2NaO_6$: 423.1527; Found: 423.1532 .

4.7.4 Experimental procedure for the synthesis of 3(2*H*)-furanone appended hydrazino-spiro[2.4]hept-5-enes from spirotricyclic olefin and 4-halo-1,3-dicarbonyl compounds: A mixture of spirotricyclic olefin (1.0 equiv.), 4-haloacetoacetate (1.5 equiv.), $[Pd(allylCl)]_2$ (5 mol%), Xphos (10 mol%) and K_2CO_3 (2.0 equiv.) was weighed in a Schlenk tube and degassed for 10 minutes. Dry THF (0.2 mM) was added and the reaction mixture was purged with argon and allowed to stir at 60 ^{o}C for 12 h. The solvent was evaporated in vacuo and the residue on silica gel (100–200 mesh) column chromatography yielded 3(2*H*)-furanone appended hydrazino-spiro[2.4]hept-5-enes

Synthesis and characterization of 3(2*H*)-furanone appended hydrazino-spiro[2.4]hept-5-enes

Diethyl 1-((4*R*,7*S*)-7-(2-ethoxy-4-oxo-4,5-dihydrofuran-3-yl)spiro[2.4]hept-5-en-4-yl)hydrazine-1,2-dicarboxylate (59a): Following the general experimental procedure, spirotricyclic olefin **5a** (100 mg, 0.38 mmol), ethyl-4-chloroacetoacetate **53a** (93 mg, 0.56 mmol), $[Pd(allyl)Cl]_2$ (7 mg, 0.02 mmol), X-phos (18 mg, 0.04 mmol) and K_2CO_3 (104 mg, 0.75 mmol) in dry THF was stirred at 60 ^{o}C for 12h. The crude product was purified over silica

gel (100-200 mesh) column chromatography (50% ethyl acetate in hexanes) to afford the desired product **55a** as pale brown viscous liquid (120 mg, 81%).



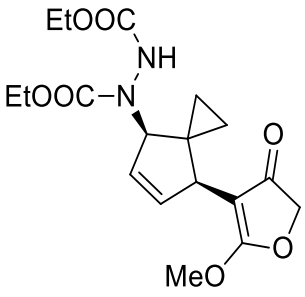
Analytical data of 55a

^{1}H NMR (500 MHz, Acetone-d_6, TMS): δ 9.28 (brs, 0.48H) 5.73-5.57 (m, 2H), 5.00-4.91 (m, 1H), 4.51-4.49 (m, 2H), 4.37 (q, *J* = 7 Hz , 1H), 4.01-3881 (m, 4H), 3.19 (brs, 1H), 1.28-1.24 (m, 3H), 1.10-1.03 (m, 6H), 0.82-0.75 (m, 1H), 0.52-0.47 (m, 1H), 0.42-0.37 (m, 1H), 0.28-0.23 (m, 1H) ppm

^{13}C{^{1}H} NMR (125 MHz, Acetone-d_6): δ 195.6, 182.0, 156.9, 156.4, 137.6, 127.9, 92.4, 74.7, 69.7, 69.5, 66.4, 61.3, 60.4, 45.1, 27.1, 17.0, 14.1, 14.0, 13.9, 9.2 ppm

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$ calcd for $C_{19}H_{26}N_2NaO_7$: 417.1632; Found: 417.1639

Diethyl 1-((4*R*,7*S*)-7-(2-methoxy-4-oxo-4,5-dihydrofuran-3-yl) spiro[2.4]hept-5-en-4-yl)hydrazine-1,2-dicarboxylate (55b): Following the general experimental procedure, spirotricyclic olefin **5a** (100 mg, 0.38 mmol), methyl-4-chloroacetoacetate **53b** (85 mg, 0.56 mmol), $[Pd(allyl)Cl]_2$ (7 mg, 0.02 mmol), X-phos (18 mg, 0.04 mmol) and K_2CO_3 (104 mg, 0.75 mmol) in dry THF was stirred at 60 ^{o}C for 12h. The crude product was purified over silica gel (100-200 mesh) column chromatography (40% ethyl acetate in hexanes) to afford the desired product **55b** as pale brown viscous liquid (107 mg, 76%)



Analytical data of 55b

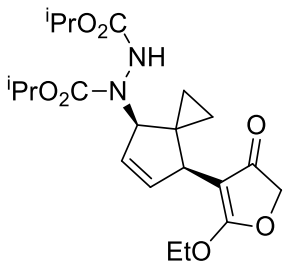
^{1}H NMR (500 MHz, Acetone-d_6, TMS): δ 9.21 (brs, 0.47H), 5.75-5.57 (m, 2H), 5.00-4.90 (m, 1H), 4.52-4.50(m, 2H), 3.99-3.90 (m, 7H), 3.19-3.18 (m, 1H), 1.10-1.03 (m, 6H), 0.81-0.77 (m, 1H), 0.54-0.47 (m, 1H), 0.41-0.36 (m, 1H), 0.30-0.22 (m, 1H) ppm

^{13}C{^{1}H} NMR (125 MHz, Acetone-d_6): δ 195.5, 182.2, 156.9, 156.5, 137.5, 127.9, 92.3, 74.7, 69.7, 61.2, 60.5, 56.3, 45.0, 27.1, 17.0, 14.1, 14.0, 9.2 ppm

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$calcd for $C_{18}H_{24}N_2NaO_7$: 403.1476; Found: 403.1472

Diisopropyl 1-((4*R*,7*S*)-7-(2-ethoxy-4-oxo-4,5-dihydrofuran-3-yl) spiro[2.4]hept-5-en-4-yl)hydrazine-1,2-dicarboxylate (55c): Following the general experimental procedure, spirotricyclic olefin **5b** (100 mg, 0.35 mmol), ethyl-4-chloroacetoacetate **53a** (88 mg, 0.53 mmol), $[Pd(allyl)Cl]_2$ (7 mg, 0.02 mmol), X-phos (17 mg, 0.04 mmol) and K_2CO_3 (98 mg, 0.71 mmol) in dry THF was stirred at 60 ^oC for 12h. The crude product was purified over silica gel (100-200 mesh) column chromatography (40% ethyl acetate in hexanes) to afford the desired product **55c** as pale-yellow viscous liquid (111 mg, 75%).

Analytical data of 55c



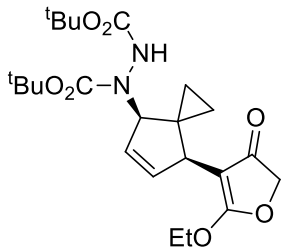
^1H NMR (500 MHz, Acetone-d_6, TMS): δ 9.04 (brs, 0.50H), 5.75-5.68 (m, 1H), 5.58-5.57 (m, 1H), 5.00-4.88 (m, 1H), 4.78-4.64 (m, 3H), 4.50-4.80 (m, 2H), 4.37 (q, *J* = 7.0 Hz, 2H), 3.19 (brs, 1H), 1.27-1.25 (m, 3H), 1.12-1.03 (m, 12H), 0.81-0.73 (m, 1H), 0.51-0.46 (m, 1H), 0.42-0.38 (m, 1H), 0.27-0.22 (m, 1H) ppm

$^{13}C\{^1H\}$ NMR (125 MHz, Acetone-d_6): δ 186.1, 172.4, 157.0, 128.4, 128.3,128.1, 126.7, 100.7, 70.8, 65.9, 60.8, 31.7, 30.8, 27.2, 24.8, 22.4, 21.3, 13.9, 13.4 ppm

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$ calcd for $C_{21}H_{30}N_2NaO_7$: 445.1945; Found: 445.1951.

Di-*tert*-butyl 1-((4*R*,7*S*)-7-(2-ethoxy-4-oxo-4,5-dihydrofuran-3-yl) spiro[2.4]hept-5-en-4-yl)hydrazine-1,2-dicarboxylate (55d): Following the general experimental procedure, spirotricyclic olefin **5c** (100 mg, 0.32 mmol), ethyl-4-chloroacetoacetate **53a** (80 mg, 0.48 mmol), $[Pd(allyl)Cl]_2$ (6 mg, 0.02 mmol), X-phos (15 mg, 0.03 mmol) and K_2CO_3 (82 mg, 0.64 mmol) in dry THF was stirred at 60 ^oC for 12h. The crude product was purified over silica gel (100-200 mesh) column chromatography (35% ethyl acetate in hexanes) to afford the desired product **55d** as pale-yellow viscous liquid (111 mg, 75%).

Analytical data of 55d



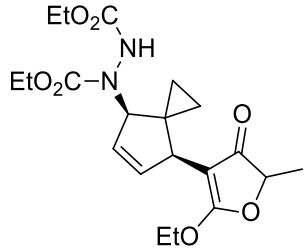
^{1}H NMR (500 MHz, Acetone-d_6, TMS): δ 8.80 (brs, 0.33H), 5.73-5.53 (m, 2H), 4.98-4.83 (m, 1H), 4.54-4.45 (m, 2H), 4.37 (m, 2H), 3.19 (brs, 1H), 1.34-1.24(m, 18H), 1.05 (brs, 3H), 0.79-0.76 (m, 1H), 0.50-0.40 (m, 2H), 0.30-0.18 (m, 1H) ppm

^{13}C{^{1}H} NMR (125 MHz, Acetone-d_6): δ 178.8, 174.5, 174.1, 156.1, 155.8, 136.0, 131.0, 100.1, 79.7, 66.2, 61.2, 57.0, 45.7, 38.2, 27.6, 27.4, 26.6, 17.7, 13.6, 9.2 ppm

HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{23}H_{34}N_2NaO_7$: 473.2258; Found: 473.2269.

Diethyl 1-((4*R*,7*S*)-7-(2-ethoxy-5-methyl-4-oxo-4,5-dihydrofuran-3-yl)spiro[2.4]hept-5-en-4-yl)hydrazine-1,2-dicarboxylate (55e): Following the general experimental procedure, spirotricyclic olefin **5a** (100 mg, 0.38 mmol), ethyl-4-chloro-3-oxopentanoate **53d** (101 mg, 0.56 mmol), $[Pd(allyl)Cl]_2$ (7 mg, 0.02 mmol), X-phos (18 mg, 0.04 mmol) and K_2CO_3 (104 mg, 0.75 mmol) in dry THF was stirred at 60 ^{o}C for 12h. The crude product was purified over silica gel (100-200 mesh) column chromatography (40% ethyl acetate in hexanes) to afford the desired product **55e** as pale-yellow viscous liquid (80 mg, 52%).

Analytical data of 55e



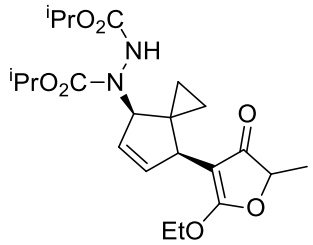
^{1}H NMR (500 MHz, Acetone-d_6, TMS): δ 9.22-9.18 (m, 0.66H), 5.75-5.53 (m, 2H), 4.99-4.87 (m, 1H), 4.60 (m, 1H), 3.99-3.91 (m, 7H), 3.17 (brs, 1H), 1.31-1.28 (m, 3H), 1.17-1.16 (m, 3H), 1.10-1.03 (m, 6H), 0.79-0.74 (m, 1H), 0.52-0.49 (m, 1H), 0.42-0.36 (m, 1H), 0.29-0.15 (m, 1H) ppm

^{13}C{^{1}H} NMR (125 MHz, Acetone-d_6): δ 197.9, 181.0, 156.8, 156.4, 137.7, 127.9, 127.8, 91.0, 83.0, 82.9, 69.7, 61.2, 60.4, 56.4, 45.0, 27.1, 17.2, 16.0, 15.9, 14.1, 14.0, 13.9, 9.2 ppm

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$ calcd for $C_{20}H_{28}N_2NaO_7$: 431.1789; Found: 431.1784

Diisopropyl 1-((4*R*,7*S*)-7-(2-ethoxy-5-methyl-4-oxo-4,5-dihydrofuran-3-yl)spiro[2.4]hept-5-en-4-yl)hydrazine-1,2-dicarboxylate (55f): Following the general experimental procedure, spirotricyclic olefin **5b** (100 mg, 0.37 mmol), ethyl-4-chloro-3-

oxopentanoate **53d** (95 mg, 0.53 mmol), $[Pd(allyl)Cl]_2$ (7 mg, 0.02 mmol), X-phos (17 mg, 0.04 mmol) and K_2CO_3 (98 mg, 0.71 mmol) in dry THF was stirred at 60 °C for 12h. The crude product was purified over silica gel (100-200 mesh) column chromatography (40% ethyl acetate in hexanes) to afford the desired product **55f** as pale-yellow viscous liquid (70 mg, 45%).



Analytical data of 55f

^{1}H NMR (500 MHz, Acetone-d_6, TMS): δ 9.15-9.10 (m, 0.54H), 5.72-5.57 (m, 2H), 5.00-4.87 (m, 1H), 4.71-4.66 (m, 2H), 4.59-4.57 (m, 1H), 4.36 (m, 2H), 3.18 (brs, 1H), 1.30-1.23 (m, 6H), 1.12-1.01 (m, 12H), 0.79-0.70 (m, 1H), 0.50-0.46 (m, 1H), 0.44-0.34 (m, 1H), 0.30-0.14 (m, 1H) ppm

$^{13}C\{^1H\}$ NMR (125 MHz, Acetone-d_6): δ 198.0, 180.6, 156.3, 156.0, 137.5, 128.0, 91.0, 82.8, 82.7, 69.6, 68.5, 67.8, 66.2, 44.8, 36.4, 27.2, 21.4, 21.3, 16.9, 16.1, 14.0, 9.1 ppm

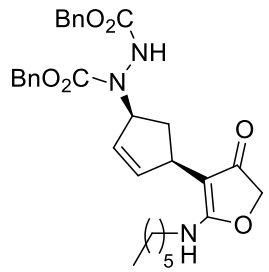
HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$ calcd for $C_{22}H_{32}N_2NaO_7$: 459.2102; Found: 459.2109

4.7.5 Experimental procedure for the synthesis of heterocyclic analogues of prostaglandins from 3-(2*H*)-furanone appended hydrazino cyclopentenes: A mixture of 3-(2*H*)-furanone appended hydrazino cyclopentene **54**/**55** (1.0 equiv.,) and amine **56** (1.1 equiv) was weighed into a dry Schlenk tube. Dry methanol (0.2 mM) was added, and the reaction mixture was stirred at 40 °C. Upon completion of the reaction, the solvent was removed, and the residue was subjected to column chromatography on neutral alumina using hexanes/ethyl acetate mixture as eluent to afford the heterocyclic analogues of prostaglandins **57** from 3-(2*H*)-furanone appended hydrazino cyclopentene.

Synthesis and characterization of heterocyclic analogues of prostaglandins

Dibenzyl 1-((1*S*,4*R*)-4-(2-(hexylamino)-4-oxo-4,5-dihydrofuran-3-yl) cyclopent-2-en-1-yl) hydrazine-1,2-dicarboxylate (**57a**): Following the general experimental procedure, 3-(2*H*)-furanone appended hydrazino cyclopentene **54h** (50 mg, 0.10 mmol) and n-hexyl amine **56a** (11 mg, 0.11 mmol) was weighed into a dry Schlenk tube. Dry methanol was added, and the reaction mixture was stirred at 40 °C for 12h. Upon completion of the reaction, the solvent

was removed, and the residue was subjected to column chromatography on neutral alumina using hexanes/ethyl acetate mixture as eluent (60% ethyl acetate in hexanes) to afford the desired product **57a** as pale-yellow viscous liquid (54 mg, 98%).



Analytical data of 57a

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.33-7.28 (m, 10H), 5.90 (brs, 1H), 5.68 (brs, 1H), 5.16-5.13 (m, 4H), 4.97 (brs, 1H), 4.46 (s, 2H), 3.74 (brs, 1H), 3.30-3.21 (m, 2H), 2.67 (brs, 1H), 1.86 (brs, 1H), 1.54-1.53 (m, 2H), 1.30-1.28 (m, 6H), 0.89 (t, *J* = 6.5Hz, 3H) ppm

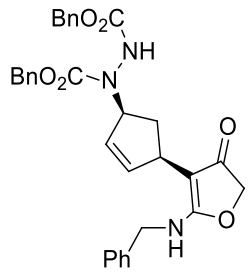
^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 191.4, 177.5, 156.7, 155.4, 135.8, 130.9, 128.6, 128.4, 128.2, 128.1, 127.7, 93.4, 74.1, 67.9, 67.7, 41.5, 35.8, 31.3, 29.9, 26.9, 26.3, 22.5, 14.0 ppm.

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$ calcd for $C_{31}H_{37}N_3NaO_6$: 570.2575; Found: 570.2579.

Dibenzyl 1-((1*S*,4*R*)-4-(2-(benzylamino)-4-oxo-4,5-dihydrofuran-3-yl)cyclopent-2-en-1-yl)hydrazine-1,2-dicarboxylate (57b): Following the general experimental procedure, 3-(2*H*)-furanone appended hydrazino cyclopentene **54h** (50 mg, 0.10 mmol) and benzyl amine **56b** (12 mg, 0.11 mmol) were weighed into a dry Schlenk tube. Dry methanol was added, and the reaction mixture was stirred at 40 °C for 12h. Upon completion of the reaction, the solvent was removed, and the residue was subjected to column chromatography on neutral alumina using hexanes/ethyl acetate mixture as eluent (70% ethyl acetate in hexanes) to afford the desired product **57b** as pale-yellow viscous liquid (52 mg, 92%).

Analytical data of 57b

^{1}H NMR (500 MHz, CD_3CN, TMS): δ 7.37-7.32 (m, 15H), 5.73-5.66 (m, 2H), 5.27-5.08 (m, 5H), 4.52-4.51 (m, 2H), 4.33 (brs, 2H), 3.48 (brs, 1H), 2.59-2.33 (m, 1H), 1.97 (brs, 1H)

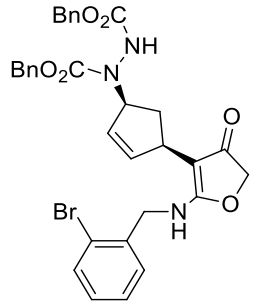


$^{13}C\{^1H\}$ NMR (125 MHz, CD_3CN): δ 192.6, 178.1, 157.5, 156.1, 137.3, 129.2, 129.0, 128.5, 128.1, 128.0, 127.8, 93.0, 74.6, 67.8, 66.9, 65.6, 45.0, 37.4, 33.1 ppm

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$ calcd for $C_{32}H_{31}N_3NaO_6$: 576.2105; Found: 576.2118.

Dibenzyl-1-((1*S*,4*R*)-4-(2-((2-bromobenzyl)amino)-4-oxo-4,5-dihydrofuran-3-yl)cyclopent-2-en-1-yl)hydrazine-1,2-dicarboxylate (57c): Following the general experimental procedure, 3-(2*H*)-furanone appended hydrazino cyclopentene **54h** (50 mg, 0.10 mmol) and 2-bromobenzyl amine **56c** (21 mg, 0.11 mmol) were weighed into a dry Schlenk tube. Dry methanol was added, and the reaction mixture was stirred at 40 °C for 24h. Upon completion of the reaction, the solvent was removed, and the residue was subjected to column chromatography on neutral alumina using hexanes/ethyl acetate mixture as eluent (70% ethyl acetate in hexanes) to afford the desired product **57c** as pale-yellow viscous liquid (46 mg, 72%).

Analytical data of 57c



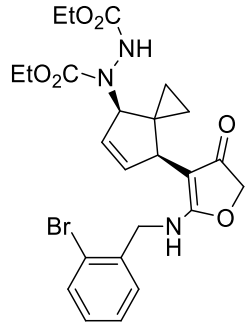
^1H NMR (500 MHz, $CDCl_3$, TMS): δ 7.49 (d, *J* = 8Hz, 1H), 7.25-7.11 (m, 13H), 5.66-5.58 (m, 2H), 5.14-4.94 (m, 5H), 4.45 (s, 2H), 4.21 (s, 2H), 3.41 (brs, 1H), 2.52-2.45 (m, 1H), 1.85 (brs, 1H) ppm

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 192.1, 177.4, 156.6, 155.4, 136.8, 135.8, 135.7, 132.9, 131.1, 129.2, 128.9, 128.5, 128.4, 128.2, 128.1, 127.8, 127.7, 122.9, 94.2, 74.2, 67.9, 67.7, 45.3, 35.7 ppm

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$ calcd for $C_{32}H_{30}N_3NaO_6Br$: 654.1210; Found: 654.1195.

Diethyl-1-((4*R*,7*S*)-7-(2-((2-bromobenzyl)amino)-4-oxo-4,5-dihydrofuran-3-yl)spiro[2.4]hept-5-en-4-yl)hydrazine-1,2-dicarboxylate (57d): Following the general experimental procedure, 3-(2*H*)-furanone appended hydrazino cyclopentene **55a** (50 mg, 0.13 mmol) and 2-bromobenzyl amine **56c** (27 mg, 0.14 mmol) were weighed into a dry Schlenk tube. Dry methanol was added, and the reaction mixture was stirred at 40 °C for 24h. Upon completion of the reaction, the solvent was removed, and the residue was subjected to column chromatography on neutral alumina using hexanes/ethyl acetate mixture as eluent (70% ethyl

acetate in hexanes) to afford the desired product **57d** as pale-yellow viscous liquid (38 mg, 55%).



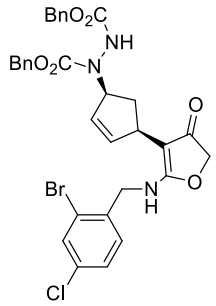
Analytical data of 57d

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.50 (d, *J* = 7.5 Hz, 1H), 7.25 (t, *J* = 7.0 Hz, 2H), 7.11 (t, *J* = 7Hz, 1H), 5.94-5.82 (m, 2H), 4.58-4.50 (m, 2H), 4.45-4.35 (m, 3H), 4.17-4.00 (m, 4H), 3.73 (brs, 1H), 1.18-1.12 (m, 7H), 0.81-0.79 (m, 2H), 0.44-0.37 (m, 1H) ppm

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 192.2, 177.8, 177.5, 157.3, 136.9, 133.5, 131.0, 129.4, 128.4, 127.8, 123.1, 74.3, 62.4, 45.4, 43.2, 29.7, 14.3, 10.5 ppm

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$calcd for $C_{24}H_{28}N_3NaO_6Br$:556.1054; Found: 556.1059

Dibenzyl 1-((1*S*,4*R*)-4-(2-((2-bromo-4-chlorobenzyl)amino)-4-oxo-4,5-dihydrofuran-3-yl)cyclopent-2-en-1-yl)hydrazine-1,2-dicarboxylate (57e): Following the general experimental procedure, 3-(2*H*)-furanone appended hydrazino cyclopentene **54h** (100 mg, 0.21 mmol) and 4-chloro-2-bromobenzyl amine **56d** (50.7 mg, 0.23 mmol) were weighed into a dry Schlenk tube. Dry methanol (1.0 mL) was added, and the reaction mixture was stirred at 40 °C for 12h. Upon completion of the reaction, the solvent was removed, and the residue was subjected to column chromatography on neutral alumina using hexanes/ethyl acetate mixture as eluent (60% ethyl acetate in hexanes) to afford the desired product **57e** as pale-yellow viscous liquid (55 mg, 50%).



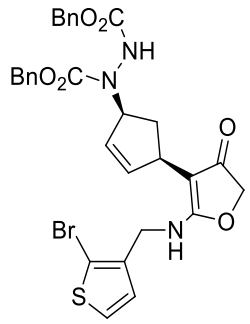
Analytical data of 57e

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.52 (s, 1H), 7.26-7.21 (m, 11H), 7.12 (d, 1H, *J*= 8Hz), 5.86 (brs, 1H), 5.65 (brs, 1H), 5.04-4.87 (m, 5H), 4.49-4.36 (m, 4H), 3.72 brs, 1H), 2.67 (brs, 1H), 1.87 (brs, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 192.1, 177.4, 156.7, 155.4, 135.7, 135.5, 134.1, 132.5, 131.2, 129.6, 128.6, 128.5, 128.4, 128.3, 128.1, 127.9, 127.7, 94.3, 74.2, 67.9, 67.8, 44.7, 35.6 ppm.

HRMS (ESI) m/z: $(M+H)^+$ calcd for $C_{32}H_{30}N_3O_6BrCl$:666.1001; Found: 666.0987

Dibenzyl 1-((1*S*,4*R*)-4-(2-(((2-bromothiophen-3-yl)methyl)amino)-4-oxo-4,5-dihydrofuran-3-yl)cyclopent-2-en-1-yl)hydrazine-1,2-dicarboxylate (57f): Following the general experimental procedure, 3-(2H)-furanone appended hydrazino cyclopentene **54h** (100 mg, 0.21 mmol) and thiophene-2-bromo-3-benzyl amine **56e** (44.2 mg, 0.23 mmol) were weighed into a dry Schlenk tube. Dry methanol (1.0 mL) was added, and the reaction mixture was stirred at 40 °C for 36h. Upon completion of the reaction, the solvent was removed, and the residue was subjected to column chromatography on neutral alumina using hexanes/ethyl acetate mixture as eluent (60% ethyl acetate in hexanes) to afford the desired product **57f** as pale-yellow viscous liquid (17 mg, 25%).

Analytical data of 57d



^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.23 (brs, 6H), 7.19 (brs, 4H), 7.10 (d, 1H, *J*= 5 Hz), 6.83 (d, 1H, *J*= 5.5 Hz), 5.80 (brs, 1H), 5.5 (brs, 1H), 5.03-4.84 (m, 5H), 4.54-4.44 (m, 2H), 4.39 (s, 2H), 3.66 (brs, 1H), 2.61 (brs, 1H), 1.81 (brs, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 192.3, 177.1, 155.1, 135.7, 135.6, 130.2, 128.6, 128.5, 128.4, 128.2, 128.1, 127.8, 109.3, 74.2, 68.0, 67.8, 39.4, 35.4 ppm.

HRMS (ESI) m/z: $(M+H)^+$ calcd for $C_{30}H_{29}N_3O_6BrS$:638.0955; Found: 638.0982

4.7.6 Experimental procedure for the intramolecular heck reaction of prostaglandins from 3-(2*H*)-furanone appended hydrazino cyclopentenes: A mixture of prostaglandin analogue of 3-(2*H*)-furanone appended hydrazino cyclopentene (1.0 equiv.), $Pd(OAc)_2$ (5 mol%), P(*o*-tol)$_3$ (10 mol%) and Et_3N (1.0 equiv.) was weighed in a Schlenk tube and degassed for 10 minutes. Dry acetonitrile (0.025 mM) was added and the reaction mixture was purged with argon and allowed to stir at 100 ºC for 12h. The solvent was evaporated in vacuo and the residue on silica gel (100–200 mesh) column chromatography yielded compound **57b.**

Following the general experimental procedure, Dibenzyl-1-((1*S*,4*R*)-4-(2-((2-bromobenzyl)amino)-4-oxo-4,5-dihydrofuran-3-yl)cyclopent-2-en-1-yl)hydrazine-1,2-

dicarboxylate **57c** (32 mg, 0.0506 mmol) $Pd(OAc)_2$ (0.51 mg, 0.0025 mmol), P(*o*-tol)$_3$ (1.6 mg, 0.0051 mmol) and Et_3N (5.1 mg, 0.0506 mmol) was weighed in a Schlenk tube and degassed for 10 minutes. Anhydrous acetonitrile (2 mL) was added and the reaction mixture was purged with argon and allowed to stir at 100 ^oC for 12h. Upon completion of the reaction, the solvent was removed, and the residue was subjected to column chromatography on on silica gel (100–200 mesh) using hexanes/ethyl acetate mixture as eluent (70% ethyl acetate in hexanes) to afford the **57b** as pale-yellow viscous liquid (18 mg, 65%). Analytical data was same as **57b.**

4.8 References

1. (a) E. Schoffers, A. Golebiowski, C. R. Johnson, *Tetrahedron* **1996**, *52*, 3769. (b) D. K. Rayabarapu, C. H. Cheng, *Acc. Chem. Res*. **2007**, *40*, 971. (c) K. V. Radhakrishnan, V. Sajisha, S. Anas, J. John, *Synlett* **2009**, 2885. (d) P. Preethanuj, E. Jijy, P. Praveen, S. Sarathchand, A. Vijayan, K. V. Radhakrishnan, J. John, *Eur. J. Org. Chem*. **2020**
2. O. Diels, J. H. Blom, W. Knoll, *Justus Liebigs Ann. Chem.* **1925**, *443*, 242.
3. D. E. Kaufmann, J. Storsberg, M. V. Nandakumar, S. Sankaranarayanan, *Adv. Synth. Catal.* **2001**, *343*, 177.
4. D. E. Kaufmann, M.-L. Yao, G. Adiwidjaja, *Angew. Chem., Int. Ed.* **2002**, *41*, 3375.
5. L. Micouin, A. P. Luna, M. Bonin, H.-P. Husson, *J. Am. Chem. Soc*. **2002**, *124*, 12098.
6. A. P. Luna, M.-A. Ceschi, M. Bonin, L. Micouin, H.-P. Husson, S. Gougeon, G. Estenne-Bouhtou, B. Marabout, M. Servin, P. George, *J. Org. Chem*. **2002**, *67*, 3522.
7. E. L. Allred, C. L. Anderson, R. L. Smith, *Tetrahedron Lett.* **1966**, *9*, 951.
8. L. Micouin, C. Bournaud, F. Chung, A. Luna, M. Pasco, G. Errasti, T. Lecourt, *Synthesis (Stuttg)*, **2009**, 869.
9. L. Micouin, C. Bournaud, T. Lecourt, C. Méliet, F. Agbossou-Niedercorn, *Eur. J. Org. Chem.*, **2008**, 2298.
10. J. M. Mellor, N. M. Smith, *J. Chem. Soc., Perkin Trans. 1*, **1984**, 2927.
11. K. V. Radhakrishnan, V. S. Sajisha, S. Anas, K. S. Krishnan, *Synlett*, **2005**, 2273.
12. K. V. Radhakrishnan, V. S. Sajisha, *Adv. Synth. Catal.* **2006**, *348*, 924.
13. E. Negishi, "Hand Book of Organopalladium Chemistry for Organic Synthesis" v*ol. 1&2*, Ed.; Wiley-Interscience, **2002**.
14. K. V. Radhakrishnan, J. John, U. Indu, E. Suresh, *J. Am. Chem. Soc.* **2009**, *131*, 5042.

15. K. V. Radhakrishnan, J. John, R. Rajan, S. Sarathchand, P. Prakash, N. Joseph, E. Suresh, *Tetrahedron* **2013**, *69*, 152.

16. S. R. Gilbertson, B. A. B. Prasad, A. E. Buechele, *Org. Lett*. **2010**, *12*, 5422.

17. P. Prakash, E. Jijy, P. Preethanuj, P. M. Pihko, S. Sarath Chand, K. V. Radhakrishnan, *Chem. - Eur. J.* **2013**, *19*, 10473.

18. S. Sarath Chand, E. Jijy, P. Prakash, J. Szymoniak, P. Preethanuj, B. P. Dhanya, K. V. Radhakrishnan, *Org. Lett.* **2013**, *15*, 3338.

19. K. V. Radhakrishnan, E. Jijy, P. Prakash, S. Saranya, E. Suresh, *Synthesis*, **2013**, *45*, 2583.

20. P. Preethanuj, V. Jijitha, A. Vijayan, J. John, K. V. Radhakrishnan, *Synthesis*, **2017**, *49*, 1816.

21. P. V. Santhini, G. Nimisha, J. John, E. Suresh, R. Luxmi Varma, K. V. Radhakrishnan, *Chem. Commun.*, **2017**, *53*, 1848.

22. P. V. Santhini, A. S. Smrithy, C. P. Irfana, S. Vaughese, J. John, K. V. Radhakrishnan, *Chem. Commun.*, **2018**, *54*, 2982.

23. A. P. Luna, M. Cesario, M. Bonin, L. Micouin, *Org. Lett.* **2003**, *5*, 4771.

24. R. Rajan, J. John, S. Thulasi, N. Joseph, K. V. Radhakrishnan, R. C. Sawant, *Synthesis* **2010**, 3649.

25. E. Jijy, P. Prakash, V. Baiju, M. Shimi, Y. Yamamoto, E. Suresh, K. V. Radhakrishnan, *Synthesis* **2014**, *46*, 2629.

26. E. Negishi, Hand Book of Organopalladium Chemistry for Organic Synthesis, Vol. 2; Ed.; Wiley-Interscience: New York, **2002**.

27. F. S. Pashkovskii, E. M. Shchukina, M. G. Gribovskii, F. A. Lakhvich, *Russ. J. Org. Chem.* **2006**, *42*, 527

28. (a) M. Sutharchanadevi, R. Murugan, 9.18 - Eight-membered Rings with One Nitrogen Atom, (Editor(s): A. R. Katritzky, C. W. Rees, E. F. V. Scriven) Comprehensive Heterocyclic Chemistry II, Pergamon, **1996**, Pages 403-428. (b) A. V. Listratova, L. G. Voskressensky, *Synthesis* **2017**, *49*, 3801.

29. Hu, D.; Grice, P.; Ley, S.V. *J. Org. Chem.* **2012**, 77, 5198.

ABSTRACT

Name of the Student**:** **Mr. Vishnu K. Omanakuttan** Registration No**.:** 10CC17A39012
Faculty of Study**:** Chemical Sciences Year of Submission**:** 2022
AcSIR academic centre/CSIR Lab**:** CSIR-National Institute for Interdisciplinary Science and Technology (CSIR-NIIST)
Name of the Supervisors**:** **Dr. Jubi John & Dr. K. V. Radhakrishnan**
Title of the thesis: ***Design and Development of Novel Synthetic Strategies towards Functionalized 3(2H)-Furanones***

The structural diversity and broad spectra of biological applications of heterocycles makes them a group of continuously researched molecules. One such attractive moiety is 3(2*H*)-furanone, a five membered oxygen containing derivative of furan. The intriguing biological responses of this heterocycle makes this as an interesting synthetic target. The first report on the synthesis of 3(2*H*)-furanone derivatives appeared in 1958, after which several research groups worked and published methods for accessing this heterocycle, which includes acids or bases mediated, organocatalysis, metal catalysis etc. The utilization of 4-halo-1,3-dicarbonyl compounds as synthetic precursor for 3(2*H*)-furanone was first established in 2012 and starting from this reagent, diverse approaches were reported for the generation of substituted 3(2*H*)-furanone. We have also contributed to the chemistry of 3(2*H*)-furanone by developing new methodologies by trapping the nucleophile generated from 4-halo-1,3-dicarbonyl compound with various electrophiles such as activated alkene, imine, dialkylazodicarboxyllate etc. The mechanistic rationalizations of the reactions mentioned above, leave something to be desired, both from the theoretical and the experimental point of view. Sustainable chemistry aspects are also lacking in most of the reported preparative methods and validation of the reactions on a bulk scale is missing. We believe that there is still large scope for developing new methods towards functionalized 3(2*H*)-furanones.

The whole thesis revolves around the utilization of 4-halo-1,3-dicarbonyl compounds as precursor for the synthesis of 3(2*H*)-furanones. The thesis is organized into four chapters. **Chapter 1** initiates with a brief introduction on the development of synthetic routes towards 3(2*H*)-furanones. **Chaper 2** disusses about the reaction of 4-halo-1,3-dicarbonyl compounds with alkynes, where we have observed the formation of 4-vinyl-3(2*H*)-furanone along with its regioisomer, irrespective of our expectation of *E*/*Z* stereoisomers. Another interesting observation was the formation of 3(2*H*)-furanone fused 2-pyridone from the reaction of 4-bromo-3-oxo-*N*-alkyl (aryl)butanamide with activated alkynes. **Chapter 3** outlines the development of a mild and metal free approach towards the synthesis of 4-aryl-3(2*H*)-furanones from our synthon 4-halo-1,3-dicarbonyl compound and benzyne precursor. The reaction proceeds *via* the nucleophilic addition of an active methylene compound to the aryne followed by ring closing of the adduct. Palladium catalyzed desymmetrization of diazabicyclic olefins *via* ring opening with active methylene nucleophile generated from 4-halo-1,3-dicarbonyl compound was investigated in **Chapter 4**. Desymmetrization of diazabicyclic olefins is an interesting and well explored area, while the reactivity of soft nucleophiles with the same is the least studied one. We have observed an interesting stereoselective synthesis of 3(2*H*)-furanones appended-1,3-*cis*-disubstituted cyclopentene from diazabicyclic olefin and 4-halo-1,3-dicarbonyls. We could extend this methodology to cyclopropane-appended spirotricyclic olefin for synthesizing 3(2*H*)-furanone substituted spiro[2.4]hept-5-ene.

List of Publications Emanating from Thesis Work

1. **Vishnu K. Omanakuttan**, Alisha Valsan C., Henning Hopf*, Jubi John*, Palladium Catalyzed Desymmetrization of Diazabicylic Olefins with 4-Halo-1,3-dicarbonyl compounds: Accessing 3(2*H*)-Furanone Appended Cyclopentenes, *Organics*, **2023**, 4, 70. (DOI:10.3390/ org4010006)
2. **Vishnu K. Omanakuttan**, Santhini P. V., Shaludheen S., Sunil Varughese, Henning Hopf*, Jubi John*, Tandem Reaction of 4-Halo-1,3-dicarbonyl Compounds with Alkynes towards 4-Vinyl-3(2*H*)-Furanones and 3(2*H*)-Furanone fused 2-Pyridones, *Asian J. Org. Chem.* **2022**. (DOI: 10.1002/ajoc.202200410)
3. **Vishnu K. Omanakuttan**, Jubi John*, Henning Hopf*, Synthesis of 3(2*H*)-Furanones: A Review, *European J. Org. Chem.*, **2021**, 163. (DOI:10.1002/ejoc.202001005)
4. Jubi John*, **Vishnu K. Omanakuttan**, Aneeja T. Cherumuttathu H. Suresh, Peter G. Jones, Henning Hopf*, Tandem α-Arylation/Cyclization of 4-Haloacetoacetates with Arynes: A Metal-Free Approach toward 4-Aryl-3-(2*H*)-furanones, *J. Org. Chem.* **2019**, 84, 5957. (DOI: 10.1021/acs.joc.9b00488)

List of Publications not Related to Thesis Work

1. Santhi Subramanyan, Deepika Selvakumar, **Vishnu K. Omanakuttan**, Kaustabh K. Maiti, Ramavarma L. Varma, Rajmohan V. Pillai, Kokkuvayil V. Radhakrishnan*, Antiproliferative potential of Amalaki Rasayana and the effect of *Buteamonosperma* (Lam.) Taub on the cytotoxicity, *Journal of Drug Research in Ayurvedic Sciences***,** **2021**,6, 218. (DOI: 10.4103/jdras.jdras_71_21)
2. Sheba A. Babu, Rajaleksshmi A. R., Nitha P. Ravi, **Vishnu K. Omanakuttan**, Rahul pulikkodan, Sunil Varughese*, Jubi John*, Unprecedented Access of Functionalized Pyrrolo[2,1-a]isoquinolines from the Domino Reaction of IsoquinoliniumYlides and Electrophilic BenzannulatedHeterocycles, ***Org. Biomol. Chem.***, **2021**, 19, 1807. (DOI: 10.1039/D1OB00005E)
3. Rahul Pulikkodan, Nitha P. Ravi, **Vishnu. K. Omanakuttan**, Sheba A. Babu, Sasikumar Parameswaran, Vakayil. K. Praveen*, Henning Hopf*, Jubi John*, Superbase-Mediated Indirect Friedländer Reaction: A Transition Metal-Free Oxidative Annulation toward Functionalized Quinolines, *European J. Org. Chem.*, **2020**, 308. (DOI: 10.1002/ejoc.202000365)

List of Conferences Presented/Participated

1. Vishnu K. Omanakuttan

International Conference on Emerging Trends in Synthetic Organic Chemistry - 2021 (ICETSOC-2021) organized by the Department of Chemistry, National Institute of Technology Puducherry, Karaikal, on December 06-07, 2021. (**Participation**)

2. Tandem α-Arylation/Cyclization of 4-Haloacetoacetates with Arynes: A Metal-Free Approach toward 4-Aryl-3-(2*H*)-furanones, **Vishnu K. Omanakuttan**, and Jubi John, Online National Conference on Organic Chemistry "NITT Organic Chemistry Conference (NITTOCC)" organized by Department of chemistry, National Institute of Technology Tiruchirappalli (NITT), on December 16 th – 18th, 2021. (**Best Poster Presentation Award in the Poster Presentation Session**)

3. Phytochemical and pharmacological evaluation of *cipadessa baccifera* leaves.

Vishnu K. Omanakuttan, Biji M., Jubi John and Radhakrishnan K. V. International Webinar on 'Phytochemistry-Impacts and Applications' and 'Prof. Dr. A. Hisham Endowment Award Function-2021', organized by Kerala Academy of Sciences (KAS) Thiruvananthapuram, on September 27th and 28th, 2021. (**Best Paper Presentation Award in the Oral Paper Presentation Session**)

4. Phytochemical investigation of *Cipadessa baccifera* Leaves.

Vishnu K. Omanakuttan, Biji M., Jubi John and Radhakrishnan K. V. International Virtual Conference, Progress and Promises in Chemical Sciences (PPCS-2020) organized by Department of chemistry, CHRIST (Deemed to be University), Bengaluru held from 15 February 2020 to 15 March 2020. (**Poster Presentation)**

5. Phytochemical investigation of *Cipadessa baccifera* Leaves.

Vishnu K. Omanakuttan, Biji M., Jubi John and Radhakrishnan K. V. International Seminar on Current Trends in Herbal Drugs and Pharma Industry, organized by College of Pharmaceutical Sciences, Govt. Medical College, Thiruvananthapuram held on March 29th to 30th, 2019 (**Poster Presentation)**

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Article

Palladium Catalyzed Ring-Opening of Diazabicylic Olefins with 4-Halo-1,3-Dicarbonyl Compounds: Accessing 3(2*H*)-Furanone-Appended Cyclopentenes

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Abstract: We have realized a Pd-catalyzed ring-opening of diazabicyclic olefins with 4-halo-1,3-dicarbonyl compounds. This reaction resulted in the formation of 3(2*H*)-furanone-appended hydrazino cyclopentenes. The reaction proceeds *via* the formation of a π-allylpalladium intermediate which is attacked by the active methylene species, and an intramolecular nucleophilic substitution in the 4-halo-1,3-dicarbonyl moiety furnishes the 3(2*H*)-furanone-substituted cyclopentene. We could extend this methodology to cyclopropane-appended spirotricyclic olefin for synthesizing 3(2*H*)-furanone-substituted spiro[2.4]hept-5-ene.

Keywords: 3(2*H*)-furanone; diazabicyclic olefins; 4-halo-1,3-dicarbonyl compounds

Citation: Omanakuttan, V.K.; Valsan, A.; Hopf, H.; John, J. Palladium Catalyzed Ring-Opening of Diazabicylic Olefins with 4-Halo-1,3-Dicarbonyl Compounds: Accessing 3(2*H*)-Furanone-Appended Cyclopentenes. *Organics* **2023**, *4*, 70–85. https://doi.org/10.3390/org4010006

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1. Introduction

Among oxygen-containing heterocyclic compounds, furanones [1–4] compose an important subclass, as it constitutes the pharmacophores of many biologically active molecules (both natural and synthetic), which covers various therapeutic categories, *viz.* analgesic, anti-inflammatory, anticancer, anticonvulsant, antibacterial, antifungal, antioxidant, antiulcer, anti-tuberculosis etc. [5]. Among the different furanones, namely (i) 2(3*H*)-furanone, (ii) 2(5*H*)-furanones, and (iii) 3(2*H*)-furanone, the later occupies a salient position because of its broad range of biological activities [6–8]. In past decades, significant attention was laid on devising synthetic routes towards substituted 3(2*H*)-furanone moieties with the ultimate aim of synthesizing natural products incorporating this heterocycle [9,10]. Different synthetic protocols for the preparation of this heterocyclic compound were reported, which included acid or base mediated, Lewis acid or base catalyzed, organocatalytic and transition-metal catalyzed transformations. In 2012, the groups of Lu and Yan independently reported the organocatalytic reaction of 4-bromoacetoacetate with nitrostyrene towards the synthesis of 4,5-disubstituted-3(2*H*)-furanones, and Yu reported an asymmetric synthesis of succinimide substituted 3(2*H*)-furanones (Figure 1) [11–13]. Soon after, our group also reported the reactions of 4-halo-1,3-dicarbonyl compounds with different electrophilic species such as activated alkene, activated imine, dialkylazodicarboxylates and arynes to access various 4,5-disubstituted-3(2*H*)-furanone derivatives (Figure 1) [14–17]. There is still immense scope for exploring the reactivity of 4-halo-1,3-dicarbonyl compounds with unexplored electrophiles for generating new scaffolds.

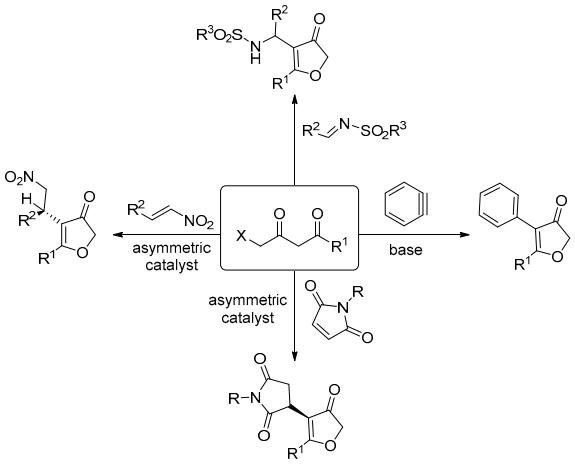


Figure 1. Synthesis of functionalized 3(2*H*)-furanones from 4-haloacetoacetate [11–16].

Diazabicyclic olefins are meso-compounds with multiple points of fracture, which upon clever ring-opening strategies can lead to highly functionalized/fused cyclopentanoids [18–21]. These heterobicyclic olefins can be easily synthesized in large quantities by the Diels Alder cycloaddition between cyclopentadiene and dialkylazodicarboxylate. The unique reactivity of these heterobicyclic olefins can be attributed to the ring strain that enables facile skeletal rearrangements under mild conditions. The initial attempts of desymmetrization involved hydroformylation, hydroboration, hydroarylation and dihydroxylation, all without ring opening of the bicyclic structure [22–27]. Mono-centered reactive species such as organometallic reagents and organic halides were later used for the ring opening of diazabicyclic olefins towards functionalized cyclopentenes [28–37]. Methodologies for cyclopentannulation with diazabicyclic olefins were then introduced by utilizing different bi-centered reactive species such as 2-iodophenol/aniline, salicylaldehyde, aryl enamides and 3-methyl 2-iodobenzoate [38–42]. In 2003, Micouin and co-workers reported the use of nucleophiles such as phenol and active methylene compounds for trapping the π-allyl palladium species generated from diazabicyclic olefin under Pd-catalysis (Figure 2a) [43]. Later, the same reactivity was extended by Radhakrishnan and co-workers to fulvene derived diazabicyclic olefins and to cyclopropane-appended spirotricyclic olefins to generate 1,4-disubstituted alkylidenecyclopentenes and *cis*-4,7-disubstituted spiro[2.4]hept-5-ene respectively [44,45]. Based on these literature reports, we hypothesized that 4-halo-1,3-dicarbonyl compounds could be used for trapping the π-allyl palladium intermediate generated from diazabicyclic olefins in the presence of Pd-catalyst for accessing 3(2*H*)-furanone-appended hydrazino cyclopentenes (Figure 2b).

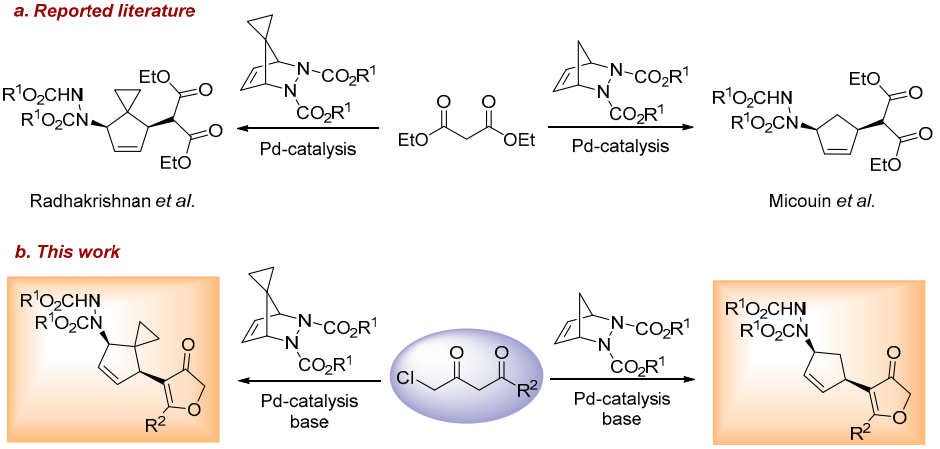


Figure 2. Pd-catalyzed ring-opening of heterobicyclic olefins with active methylene compounds. (**a**) Reported literature; (**b**) This work.

2. Results and Discussion

We planned to assess our hypothesis by taking diazabicyclic olefin **1a** and ethyl-4-chloro acetoacetate **2a** as substrates. The initial reaction was set up with 1.0 equivalent of **1a** and 1.5 equivalents of **2a** in the presence of $Pd(OAc)_2$ as the catalyst, dppf as ligand and K_2CO_3 as base in THF at 60 °C. After 12 h, we could isolate the expected 3(2*H*)-furanone-appended hydrazino cyclopentene **3a** in 10% yield from the reaction mixture (Figure 3). The structure of **3a** was assigned based on ^{1}H NMR, ^{13}C NMR, high resolution mass spectral analyses and on comparison with literature reports [43–45].

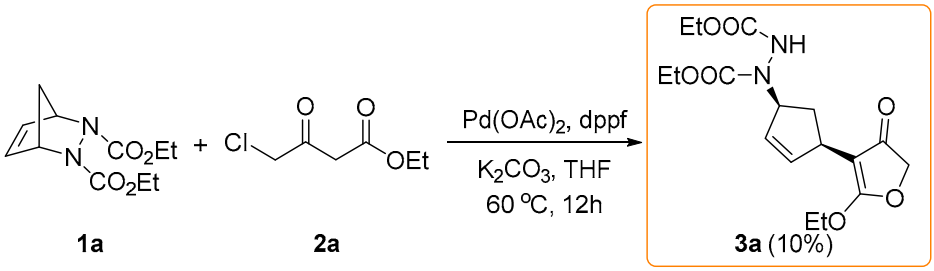


Figure 3. Pd-catalyzed ring-opening of diazabicyclic olefin **1a** with ethyl-4-chloro acetoacetate **2a**.

In the HMBC spectrum of **3a** (spectrum in SI), the proton signal at 3.40–3.42 ppm (1′) showed correlations with C5, C4 and C3 carbons (Figure 4). These relations confirmed the connectivity of cyclopentene moiety with 3(2*H*)-furanone core. The *cis* stereochemistry at the 1′ and 4′ positions was confirmed through the NOE analysis (spectrum in SI) and in comparison with the literature reports [43–45]. When we irradiated the signal at 3.40–3.42 ppm, a signal enhancement in the opposite phase was observed at 5.32 ppm. This confirmed the stereochemistry of protons at 3.40–3.42 and 5.32 ppm as in the same phase.

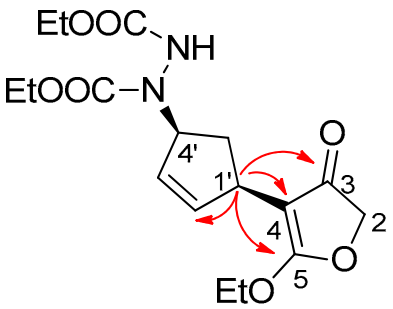


Figure 4. Selected HMBC correlations of **3a**.

The optimization of the Pd-catalyzed ring opening of diazabicyclic olefin with 4-halo-1,3-dicarbonyl compounds was carried out with **1a** and **2a** as substrates. We started with the screening of Pd-catalysts such as $Pd(OAc)_2$, $Pd(OCOCF_3)_2$, $Pd(PPh_3)_4$, $(Pd(allyl)Cl)_2$, $PdCl_2$ and $Pd(dba)_3.CHCl_3$ among which the $(Pd(allyl)Cl)_2$ catalyzed reaction afforded the 3(2*H*)-furanone-appended hydrazino cyclopentene **3a** in 32% yield (Table 1, entries 1–6). We then checked the efficiency of different ligands like dppf, dppe, dppp, XPhos and DevPhos, from which XPhos was found to be the best option (Table 1, entries 4, 7–10). A base screen revealed that K_2CO_3 was superior to other bases like Na_2CO_3, Cs_2CO_3, NaH and NaO^{t}Bu (Table 1, entries 9, 11–14). Finally, we examined different solvents such as THF, CH_3CN, toluene, 1,4-dioxane and DCE among which **3a** was isolated in 85% yield from the reaction with DCE as the medium (Table 1, entries 9, 15–18).

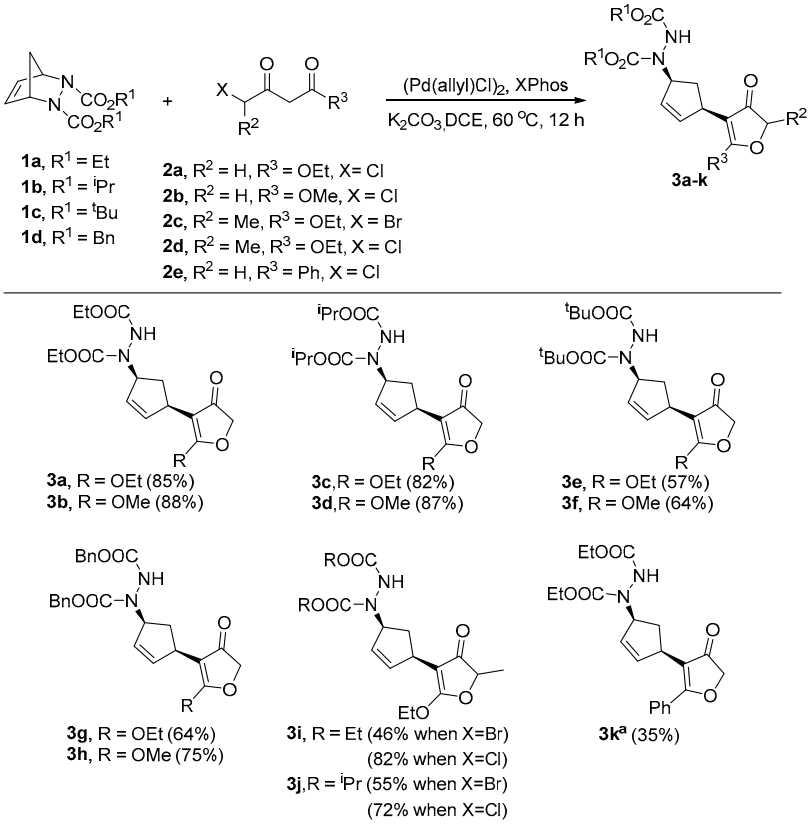
Table 1. Optimization studies.

Entry	Catalyst	Ligand	Base	Solvent	Yield
1	$Pd(OAc)_2$	dppf	K_2CO_3	THF	10
2	$Pd(OCOCF_3)_2$	dppf	K_2CO_3	THF	20
3	$Pd(PPh_3)_4$	dppf	K_2CO_3	THF	15
4	$(Pd(allyl)Cl)_2$	dppf	K_2CO_3	THF	32
5	$PdCl_2$	dppf	K_2CO_3	THF	28
6	$Pd(dba)_3.CHCl_3$	dppf	K_2CO_3	THF	23
7	$(Pd(allyl)Cl)_2$	dppe	K_2CO_3	THF	10
8	$(Pd(allyl)Cl)_2$	dppp	K_2CO_3	THF	34
9	$(Pd(allyl)Cl)_2$	XPhos	K_2CO_3	THF	55
10	$(Pd(allyl)Cl)_2$	DevPhos	K_2CO_3	THF	43
11	$(Pd(allyl)Cl)_2$	XPhos	Na_2CO_3	THF	51
12	$(Pd(allyl)Cl)_2$	XPhos	Cs_2CO_3	THF	32
13	$(Pd(allyl)Cl)_2$	XPhos	NaH	THF	NR
14	$(Pd(allyl)Cl)_2$	XPhos	NaO^tBu	THF	25
15	$(Pd(allyl)Cl)_2$	XPhos	K_2CO_3	CH_3CN	68
16	$(Pd(allyl)Cl)_2$	XPhos	K_2CO_3	Toluene	47
17	$(Pd(allyl)Cl)_2$	XPhos	K_2CO_3	1,4-Dioane	58
18	$(Pd(allyl)Cl)_2$	XPhos	K_2CO_3	DCE	85

Reaction conditions: **1a** (1.0 equiv., 0.42 mmol), **2a** (1.5 equiv., 0.62 mmol), base (2.0 equiv.), catalyst (5 mol%), ligand (10 mol%), solvent (2.0 mL), 60 °C, 12 h; isolated yields.

The optimized conditions for the Pd-catalyzed synthesis of 3(2*H*)-furanone-appended hydrazino cyclopentene was found to be 1.0 equivalent of diazabicyclic olefin **1**, 1.5 equivalents of 4-halo-1,3-dicarbonyl compound **2**, 2.0 equivalents of K_2CO_3, 5 mol% of $(Pd(allyl)Cl)_2$, 10 mol% of XPhos in DCE (solvent) at 60 °C for 12 h. Under these conditions, the generality of the 3(2*H*)-furanone-appended 3,5-disubstituted cyclopentene synthesis was studied with different diazabicyclic olefins and of 4-halo-1,3-dicarbonyl compounds (Figure 5). The reactions of diazabicyclic adduct **1a** with ethyl-4-chloro acetoacetate **2a** and methyl-4-chloro acetoacetate **2b** afforded the corresponding products **3a** and **3b** in 85% and 88% yields, respectively. In a similar way, the reactions of bicyclic adduct **1b** (derived from cyclopentadiene and diisopropylazodicarboxylate) with **2a** and **2b** furnished the products **3c** and **3d** in excellent yields. There was a decrease in yield for 3(2*H*)-furanone-appended hydrazino cyclopentenes **3e** (57%), **3f** (64%), **3g** (64%) and **3h** (75%) synthesized from bicyclic adducts **1c** and **1d**. The Pd-catalyzed reactions of ethyl 4-bromo-3-oxopentanoate **2c** with bicyclic adducts **1a** and **1b** were found to afford the products **3i** and **3j** in satisfactory yields (as a mixture of diastereomers) whereas the use of 4-chloro-3-oxopentanoate **2d** instead of **2c** resulted in better reactions affording **3i** and **3j** in good to excellent yields. A phenyl moiety was introduced to the fifth position of 3(2*H*)-furanone moiety of **3k** by starting from 4-chloro-1-phenylbutane-1,3-dione **2e** and bicyclic adduct **1a**.

Having established a methodology for accessing 3(2*H*)-furanone-appended hydrazino cyclopentene from diazabicyclic olefins and 4-halo-1,3-dicarbonyl compounds, we were interested in expanding the scope of olefins used. In this line we checked the reactivity of spirotricyclic olefin **4a** (derived from spiro[2.4]hepta-4,6-diene and diethylazodicarboxylate) with ethyl-4-chloro acetoacetate **2a** under the optimized conditions developed for diazabicyclic olefin. As expected the 3(2*H*)-furanone-substituted hydrazino-spiro[2.4]hept-5-ene **5a** was isolated from the reaction in 12% yield (Figure 6). A significant improvement in the yield of **5a** to 81% was observed when the solvent was changed from DCE to THF.



Reaction conditions: **1** (1.0 equiv., 1.05 mmol), **2** (1.5 equiv., 1.58 mmol), K_2CO_3 (2.0 equiv.), $(Pd(allyl)Cl)_2$ (5 mol%), XPhos (10 mol%), DCE (5.0 mL), 60 °C, 12 h, isolated yields. [**a**] rt.

Figure 5. Generality of 3(2*H*)-furanone-appended hydrazino cyclopentene synthesis from diazabicyclic olefins and of 4-halo-1,3-dicarbonyl compounds.

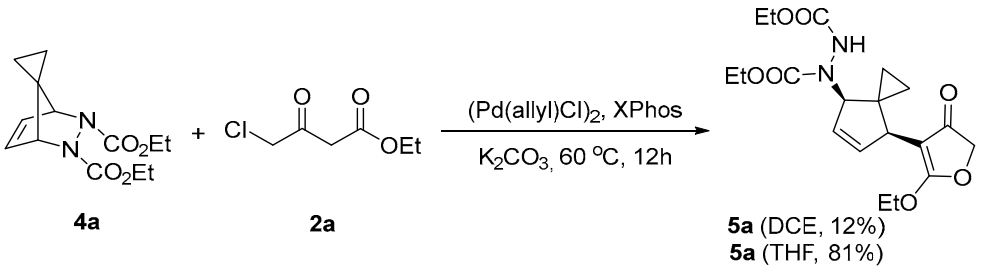
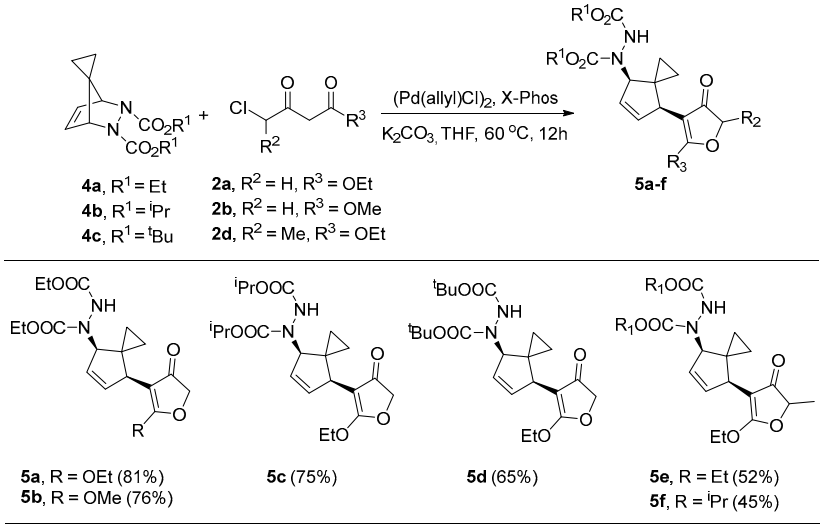


Figure 6. Pd-catalyzed ring-opening of spirotricyclic olefin (**4a**) with ethyl-4-chloro acetoacetate (**2a**).

The generality of the Pd-catalyzed ring opening of spirotricyclic olefins with 4-halo-1,3-dicarbonyl compounds were then investigated (Figure 7). The reactions of the olefins **4a**–**4c** with 4-chloro-ethyl/methyl acetoacetates **2a**–**2b** afforded the corresponding 3(2*H*)-furanone-substituted hydrazino-spiro[2.4]hept-5-enes **5a** to **5d** in good to excellent yields. The reactions of 4-chloro-3-oxopentanoate **2d** with spirotricyclic olefins **4a** & **4b** also afforded the expected products **5e** and **5f** (as a mixture of diastereomers) in 52% and 45% yields, respectively.



Reaction conditions: **4** (1.0 equiv., 1.05 mmol), **2** (1.5 equiv., 1.58 mmol), K_2CO_3 (2.0 equiv.), $(Pd(allyl)Cl)_2$ (5 mol%), XPhos (10 mol%), THF (5.0 mL), 60 °C, 12 h, Isolated yields.

Figure 7. Generality of 3(2H)-furanone-substituted hydrazino-spiro[2.4]hept-5-ene synthesis from diazabicyclic olefins and of 4-halo-1,3-dicarbonyl compounds.

We propose a mechanism for the Pd-catalyzed synthesis of 3(2*H*)-furanone-appended hydrazino cyclopentene from diazabicyclic olefin and 4-halo acetoacetate based on literature precedents (Figure 8) [43–46].

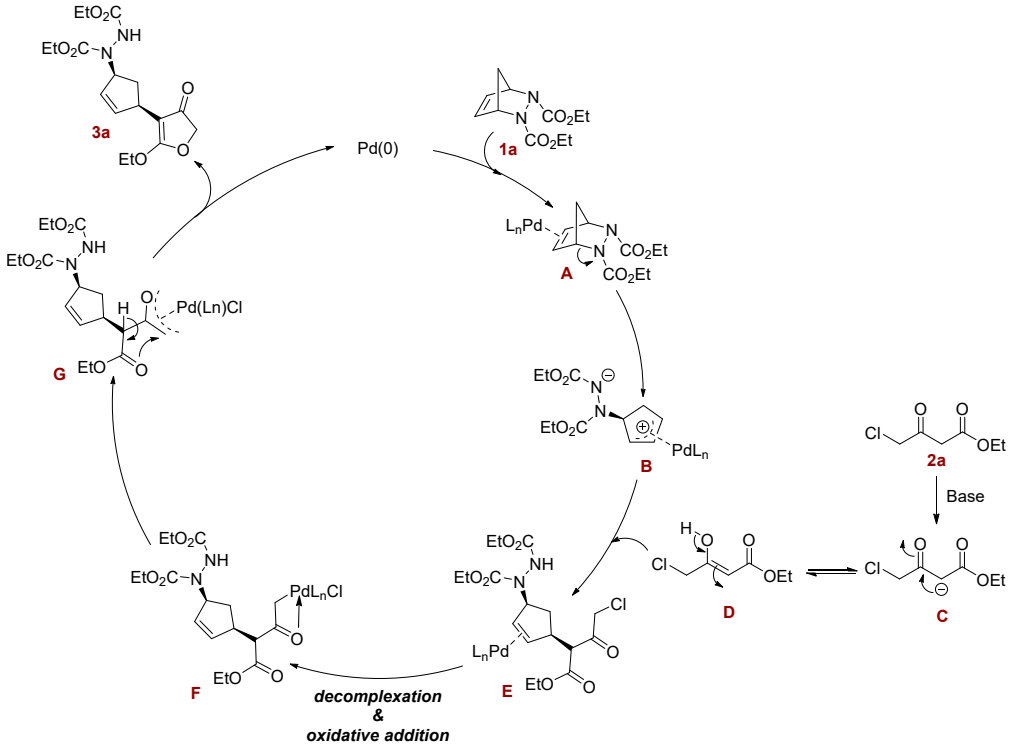
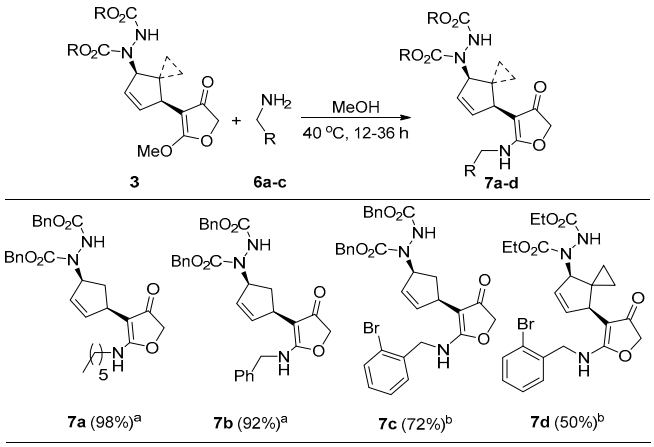


Figure 8. Proposed mechanism for the Pd-catalyzed ring-opening of azabicyclic olefin with 4-halo acetoacetate.

The reaction proceeds through three stages; the first one being the attack of Pd(0) species to the double bond (through *exo*-face) of the diazabicyclic olefin **1a** to form the π-allylpalladium intermediate **B** (via **A**) by the cleavage of one C-N bond (*endo* phase). The second stage involves the attack of the anionic species **C** or **D** (generated from **2a**) to one end of the π-allylpalladium intermediate (through the opposite side of that of Pd) **B** generating the species **E**. Then, the decomplexation of Pd-species from the cyclopentene ring occurs, followed by the oxidative addition of Pd(0)Ln to the C–Cl bond to form **F**. The intermediate **F** is easily converted into oxy-π-allylpalladium intermediate **G** and the ester enolate formed by the abstraction of the acidic proton attacks the carbon end of the oxy-π-allyl Pd-intermediate resulting in the 3(2*H*)-furanone ring. The classical double inversion mechanism is the reason for the *cis*-stereochemistry in the product.

Our next attempt was to utilize the synthesized 3(2*H*)-furanone-appended hydrazino cyclopentenes for the generation of biologically relevant furanone-analogues [47,48]. This transformation was effected by treating the 3(2*H*)-furanone-appended hydrazino cyclopentene **3** with an amine **6** in MeOH at 40 °C. These reactions were found to be completed in 12 to 24 h, from which the respective furanone-analogues **7a–d** were isolated in moderate to excellent yields (Figure 9).



Reaction conditions: [a] **3** (1.0 equiv.), **6** (1.1 equiv.), MeOH (0.2 mM), 40 °C, 12 h, Isolated yields; [b] 24 h.

Figure 9. Generality of amine-functionalized 3(2H)-furanone-appended hydrazino cyclopentene synthesis.

During the synthesis of amine-functionalized 3(2*H*)-furanone derivatives, we chose different *ortho*-bromo-benzylamines to access scaffolds that can be subjected to further transformations towards complex fused moieties. We hypothesized that, by subjecting compound **7c** to intramolecular Heck coupling conditions, a tri-ring-fused azocine moiety, namely 3(2*H*)-furanone-fused cyclopetano-benzoazocine could be synthesized. The first trial run of the intramolecular Heck coupling of **7c** was carried out with $Pd(OAc)_2$ as the catalyst, P(*o*-tol)$_3$ as the ligand, and Et_3N as the base in CH_3CN at 100 °C (Figure 10). After 12 h, to our dismay, we isolated the dehalogenated 3(2*H*)-furanone **7b**. We then changed different conditions to see if the expected 3(2*H*)-furanone-fused cyclopetano-benzoazocine could be synthesized [49]. All the attempts were in vain, furnishing the dehalogenated product. The reason for failure might be due to the fact that oxidatively added palladium species might not be in a bonding distance with that of the alkene (of cyclopentene) for insertion reaction.

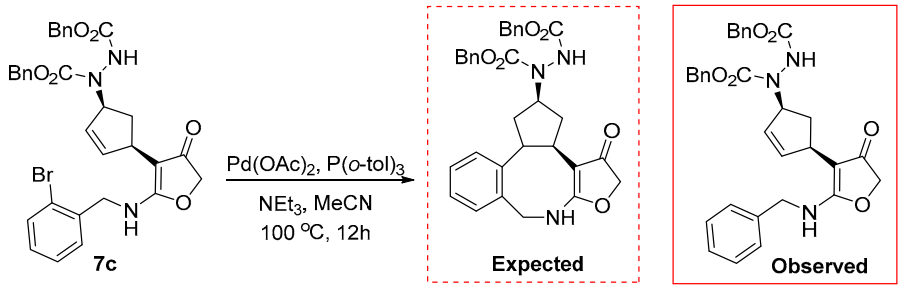


Figure 10. Attempted intramolecular Heck coupling of amine-functionalized 3(2*H*)-furanone derivatives towards 3(2*H*)-furanone-fused tetrahydroazocine derivative.

3. Materials and Methods

All chemicals were of the best grade commercially available and were used without further purification. All solvents were purified according to the standard procedures; dry solvents were obtained according to the literature methods and stored over molecular sieves. Analytical thin-layer chromatography was performed on polyester sheets precoated with silica gel containing fluorescent indicator (POLYGRAMSIL G/UV254). Gravity column chromatography was performed using silica, and mixtures of ethyl acetate hexanes were used for elution. Melting points were measured with a Fisher John melting point apparatus and are uncorrected. NMR spectra were recorded with Bruker Avance-500 (500 MHz for ^{1}H NMR, 125 MHz for ^{13}C NMR) spectrophotometer instruments. All spectra were measured at 300 K, unless otherwise specified. The chemical shifts δ are given in ppm and referenced to the external standard TMS or internal solvent standard. ^{1}H NMR coupling constants (*J*) are reported in Hertz (Hz) and multiplicities are indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and qdd (doublet of doublets). Mass spectra were performed with a Thermo Finnigan MAT95XL, a Thermo Fisher Scientific LTQ Orbitrap Velos, and an Agilent 6890 gas chromatograph with JMS-T100GC spectrometer or with a ESI/HRMS at 60,000 resolution using Thermo Scientific Exactive mass spectrometer with orbitrap analyzer.

All chemicals were purchased from TCI Chemicals (India), Sigma-Aldrich (Merck-India) or Spectrochem (India).

4-Bromoacetoacetates and 4-Chlorooacetoacetates were prepared by the reported procedures [50–52].

The synthesized 3(2*H*)-furanone-appended cyclopentenes contains hydrazide moieties, and the peaks in ^{1}H and ^{13}C NMR spectra were broadened (or doubled) by the presence of amide rotamers [53].

Experimental procedure for the synthesis of 3(2*H*)-furanone-appended hydrazino cyclopentene**:** A mixture of diazabicyclic olefin (1.0 equiv.), 4-haloacetoacetate (1.5 equiv.), $[Pd(allylCl)]_2$ (5 mol%), Xphos (10 mol%) and K_2CO_3 (2.0 equiv.) was weighed into a dry Schlenk tube and degassed for 10 min. Dry DCE (0.2 mM) was added and the reaction mixture was purged with argon and allowed to stir at 60 °C for 12 h. The solvent was evaporated in vacuo and the residue on silica gel (100–200 mesh) column chromatography using mixtures of hexanes/ethyl acetate as eluents, affording the corresponding 3(2*H*)-furanone-appended hydrazino cyclopentene.

Synthesis and characterization of 3(2*H*)-furanone-appended hydrazino cyclopentenes **3a** to **3k**:

Diethyl-1-((1*S*,4*R*)-4-(2-ethoxy-4-oxo-4,5-dihydrofuran-3-yl)cyclopent-2-en-1-yl)hydrazine-1,2-dicarboxylate (**3a**): The reaction was performed according to the general procedure with diazabicyclic olefin (derived from cyclopentadiene and diethylazadicarboxylate) **1a** (100 mg, 0.42 mmol), ethyl-4-chloroacetoacetate **2a** (103 mg, 0.62 mmol), $[Pd(allyl)Cl]_2$ (8 mg, 0.02 mmol), Xphos (20 mg, 0.04 mmol) and K_2CO_3 (115 mg, 0.83 mmol) in dry DCE was stirred at 60 °C for 12 h. Upon completion of the reaction as indicated by TLC, the solvent was removed and the crude product was purified over silica gel (100–200 mesh)

column chromatography (70% ethyl acetate in hexanes) to afford the product **3a** as pale-yellow viscous liquid (130 mg, 85%). Analytical data of **3a**: FTIR (ν_{max} in cm^{-1}): 3307, 2983, 2936, 1712, 1468, 1411, 1375, 1231, 1118, 1104, 1040, 953, 762, 663, 565. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 5.65–5.57 (m, 2H), 5.32 (brs, 1H), 4.46 (s, 2H), 4.42–4.38 (m 2H), 4.11 (brs, 5H), 3.42–3.40 (m, 1H), 2.51 (brs, 1H), 1.84 (brs, 1H), 1.37 (t, *J* = 7.0 Hz, 3H), 1.21–1.16 (m, 6H) ppm. ^{13}C NMR (125 MHz, CDCl3): δ 195.8, 181.2, 156.8, 156.1, 136.6, 129.0, 128.4, 95.2, 74.7, 66.2, 62.2, 61.5, 36.4, 32.8, 14.7, 14.5 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{17}H_{24}N_2NaO_7$: 391.1476; found: 391.1486

The remaining reactions were performed following this general procedure.

Diethyl-1-((1*S*,4*R*)-4-(2-methoxy-4-oxo-4,5-dihydrofuran-3-yl)cyclopent-2-en-1-yl) hydrazine-1,2-dicarboxylate (**3b**): Pale yellow viscous liquid (131 mg, 88%); ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 5.64- 5.58 (m, 2H), 5.31 (brs, 1H), 4.48 (s, 2H), 4.11 (brs, 5H), 4.00 (s, 3H), 3.42–3.38 (m, 1H), 2.51 (brs, 1H), 1.82–1.80 (m, 1H), 1.20–1.16 (m, 6H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 195.8, 181.4, 156.8, 156.0, 136.5, 128.9, 128.5, 95.3, 74.8, 66.6, 64.1, 62.1, 61.5, 56.4, 36.2, 32.7, 14.5 ppm; HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{16}H_{22}N_2NaO_7$: 377.1319; found: 377.1364

Diisopropyl-1-((1*S*,4*R*)-4-(2-ethoxy-4-oxo-4,5-dihydrofuran-3-yl)cyclopent-2-en-1-yl) hydrazine-1,2-dicarboxylate (**3c**): Yellow viscous liquid (122 mg, 82%); FTIR (ν_{max} in cm^{-1}): 3306, 2988, 2929, 1713, 1388, 1363, 1312, 1254, 1162, 1045, 1023, 964, 866, 778, 754. 1H NMR (500 MHz, $CDCl_3$, TMS): δ 5.66–5.58 (m, 2H), 5.33 (brs, 1H), 4.93–4.85 (m, 2H), 4.47–4.37 (m, 5H), 3.42–3.40 (m, 1H), 2.49–2.47 (m, 1H), 1.93 (brs, 1H), 1.36 (t, *J* = 7.0 Hz, 3H), 1.19–1.17 (m, 12H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 195.7, 181.2, 156.3, 155.6, 136.9, 136.3, 129.2, 128.6, 95.2, 74.6, 69.5, 69.0, 66.3, 66.1, 63.8, 36.2, 29.2, 22.1, 22.0, 14.8 ppm; HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{19}H_{28}N_2NaO_7$ 419.1789; found: 419.1782.

Diisopropyl-1-((1*S*,4*R*)-4-(2-methoxy-4-oxo-4,5-dihydrofuran-3-yl)cyclopent-2-en-1-yl) hydrazine-1,2-dicarboxylate (**3d**): Yellow viscous liquid (130 mg, 87%); ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 5.65- 5.58 (m, 2H), 5.32 (brs, 1H), 4.86–4.85 (m, 2H), 4.48 (s, 2H), 3.99 (s, 3H), 3.41 (brs, 1H), 2.46 (brs, 1H), 1.80 (brs, 1H), 1.18–1.17 (m, 12H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 195.6, 181.4, 156.3, 155.6, 155.5, 136.1, 129.2, 128.7, 95.9, 95.2, 74.7, 69.5, 69.1, 63.7, 56.5, 56.3, 36.1, 35.9, 32.7, 32.1, 22.1, 21.9 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{18}H_{26}N_2NaO_7$: 405.1632; found: 405.1640.

Di-*tert*-butyl 1-((1*S*,4*R*)-4-(2-ethoxy-4-oxo-4,5-dihydrofuran-3-yl)cyclopent-2-en-1-yl) hydrazine-1,2-dicarboxylate (**3e**): Yellow viscous liquid (82 mg, 57%); FTIR (ν_{max} in cm^{-1}): 3308, 2971, 2922, 1721, 1396, 1372, 1323, 1249, 1164, 1054, 1018, 862, 763. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 5.66–5.61 (m, 2H), 5.28–5.14 (m, 1H), 4.52–4.37 (m, 5H), 3.40 (m, 1H), 2.44 (s, 1H), 1.78 (brs, 3H), 1.38–1.37 (m, 18H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 195.7, 181.3, 155.1, 154.8, 135.4, 129.7, 95.4, 80.6, 74.7, 66.0, 36.1, 31.9, 28.2, 28.0, 14.6 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{21}H_{32}N_2NaO_7$: 447.2102; found: 447.2089.

Di-*tert*-butyl 1-((1*S*,4*R*)-4-(2-methoxy-4-oxo-4,5-dihydrofuran-3-yl)cyclopent-2-en-1-yl)hydrazine-1,2-dicarboxylate (**3f**): Yellow viscous liquid (89 mg, 64%); ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 5.64 (brs, 2H), 5.28 (brs, 1H), 4.46 (s, 2H), 3.98 (s, 3H), 3.40 (s, 1H), 2.44 (brs, 1H), 1.83 (brs, 1H), 1.39–1.38 (m, 18H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 195.7, 181.3, 155.5, 155.0, 135.7, 129.7, 95.7, 81.0, 80.6, 74.7, 56.4, 56.2, 36.1, 33.1, 32.0, 29.7, 28.3 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{20}H_{30}N_2NaO_7$: 433.1945; found: 433.1961.

Dibenzyl 1-((1*S*,4*R*)-4-(2-ethoxy-4-oxo-4,5-dihydrofuran-3-yl)cyclopent-2-en-1-yl) hydrazine-1,2-dicarboxylate (**3g**): Brown viscous liquid (90 mg, 64%); FTIR (ν_{max} in cm^{-1}): 3278, 3069, 3040, 2965, 1712, 1567, 1498, 1417, 1306, 1254, 1219, 1244, 1080, 1045, 750, 704, 599. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.24–7.19 (m, 10H), 5.62–5.32 (m, 3H), 5.08–4.99 (m, 4H), 4.48–4.36 (m, 4H), 3.39 (s, 1H), 2.51 (brs, 1H), 1.91 (brs, 1H), 1.35–1.32 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 195.9, 181.3, 156.8, 156.5, 155.8, 137.1, 136.3, 128.7, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.6, 127.4, 95.0, 74.7, 67.5, 67.1, 66.8, 66.4, 64.3, 36.6, 32.3, 14.7 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{27}H_{28}N_2NaO_7$: 515.1782; found: 515.1789.

Dibenzyl 1-((1*S*,4*R*)-4-(2-methoxy-4-oxo-4,5-dihydrofuran-3-yl)cyclopent-2-en-1-yl) hydrazine-1,2-dicarboxylate (**3h**): brown viscous liquid (98 mg, 75%); ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.24–7.21 (m, 10H), 5.62–5.38 (m, 3H), 5.08–4.99 (m, 4H), 4.50–4.39 (m, 2H), 3.96 (brs, 3H), 3.39 (s, 1H), 2.50 (brs, 1H), 1.84 (brs, 1H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 195.8, 181.4, 156.7, 155.8, 136.9, 136.3, 128.8, 128.4, 128.4, 128.0, 127.9, 95.1, 74.8, 67.6, 67.1, 64.3, 56.3, 36.4, 32.3 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{26}H_{26}N_2NaO_7$: 501.1632; found: 501.1625

Diethyl 1-((1*S*,4*R*)-4-(2-ethoxy-5-methyl-4-oxo-4,5-dihydrofuran-3-yl)cyclopent-2-en-1-yl)hydrazine-1,2-dicarboxylate (**3i**): Yellow viscous liquid (130 mg, 82%); ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 5.64–5.56 (m, 2H), 5.32 (brs, 1H), 4.57–4.54 (m, 1H), 4.38–4.36 (m, 2H), 4.14–4.11 (m, 4H), 3.41–3.39 (m, 1H), 2.50 (brs, 1H), 1.90 (m, 1H), 1.41–1.40 (m, 3H), 1.36 (t, *J* = 7.0 Hz, 3H), 1.18–1.15 (m, 6H) ppm;^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 198.6, 180.0, 156.9, 156.1, 137.0, 128.8, 93.7, 82.9, 75.5, 66.1, 62.1, 36.5, 30.9, 29.7, 16.5, 14.7, 14.5 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{18}H_{26}N_2NaO_7$: 405.1632; found: 405.1629.

Diisopropyl 1-((1*S*,4*R*)-4-(2-ethoxy-5-methyl-4-oxo-4,5-dihydrofuran-3-yl)cyclopent-2-en-1-yl)hydrazine-1,2-dicarboxylate (**3j**): yellow viscous liquid (115 mg, 72%); FTIR (ν_{max} in cm^{-1}): 3301, 2975, 2936, 1712, 1696, 1527, 1486, 1405, 1299, 1263, 1179, 1115, 1056, 941, 761, 611. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 5.65–5.56 (m, 2H), 5.34 (brs, 1H), 4.91–4.85 (m, 2H), 4.52–4.51 (m, 1H), 4.38–4.37 (m, 2H), 3.40 (brs, 1H), 2.46 (brs, 1H), 1.92 (brs, 1H), 1.41–1.34 (m, 6H), 1.18 (brs, 12H) ppm;^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 198.4, 179.9, 156.4, 155.7, 136.6, 129.0, 128.4, 93.5, 82.9, 69.5, 66.0, 36.5, 32.3, 22.1, 22.0, 16.6, 14.8 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{20}H_{30}N_2NaO_7$: 433.1945; found: 433.1956.

Diethyl 1-((1*S*,4*R*)-4-(4-oxo-2-phenyl-4,5-dihydrofuran-3-yl)cyclopent-2-en-1-yl) hydrazine-1,2-dicarboxylate (**3k**): (This reaction was performed at rt) pale yellow viscous liquid (90 mg, 35%); FTIR (ν_{max} in cm^{-1}): 3331, 2976, 2936, 1701, 1596, 1410, 1381, 1266, 1231, 1167, 1144, 1069. 947. 821, 761, 704, 651, 501, 431. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.77–7.73 (m, 2H), 7.45 (brs, 1H), 7.43–7.20 (m, 2H), 5.99 (s, 1H), 5.79–5.73 (m, 2H), 4.22–4.17 (m, 2H), 4.11–4.10 (m, 5H), 3.15 (brs, 1H), 2.52 (brs, 1H), 1.94 (brs, 1H), 1.25–1.13 (m, 6H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 203.3, 185.9, 155.8, 154.4, 152.2, 132.8, 128., 127.1, 101.5, 87.3, 62.9,62.5, 62.0, 46.5, 30.9, 2.7, 14.5,14.1,14.1 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{21}H_{24}N_2NaO_6$: 423.1527; found: 423.1532.

Experimental procedure for the synthesis of 3(2*H*)-furanone-appended hydrazino-spiro[2.4]hept-5-enes from spirotricyclic olefin and 4-halo-1,3-dicarbonyl compounds: A mixture of spirotricyclic olefin (1.0 equiv.), 4-haloacetoacetate (1.5 equiv.), $[Pd(allylCl)]_2$ (5 mol%), Xphos (10 mol%) and K_2CO_3 (2.0 equiv.) was weighed in a Schlenk tube and degassed for 10 min. Dry THF (0.2 mM) was added and the reaction mixture was purged with argon and allowed to stir at 60 °C for 12h. The solvent was evaporated in vacuo and the residue on silica gel (100–200 mesh) column chromatography yielded 3(2*H*)-furanone-appended hydrazino-spiro[2.4]hept-5-enes.

Synthesis and characterization of 3(2*H*)-furanone-appended hydrazino-spiro[2.4]hept-5-enes:

Diethyl 1-((4*R*,7*S*)-7-(2-ethoxy-4-oxo-4,5-dihydrofuran-3-yl)spiro[2.4]hept-5-en-4-yl) hydrazine-1,2-dicarboxylate (**5a**): Following the general experimental procedure, spirotricyclic olefin **4a** (derived from spiro[2.4]hepta-4,6-diene and diethylazodicarboxylate) (100 mg, 0.3755 mmol), ethyl-4-chloroacetoacetate **2a** (92.7 mg, 0.56 mmol), $[Pd(allyl)Cl]_2$ (7 mg, 0.02 mmol), Xphos (18 mg, 0.04 mmol) and K_2CO_3 (104 mg, 0.75 mmol) in dry THF (1.9 mL) was stirred at 60 °C for 12h. The crude product was purified over silica gel (100–200 mesh) column chromatography (50% ethyl acetate in hexanes) to afford the desired product **5a** as pale brown viscous liquid (120 mg, 81%). Analytical data of **5a:** FTIR (ν_{max} in cm^{-1}): 3289, 2959, 222, 2861, 1697, 1412, 1309, 1263, 1118, 1024, 966, 798. ^{1}H NMR (500 MHz, Acetone-d_6, TMS): δ 9.28 (brs, 0.48H) 5.73–5.57 (m, 2H), 5.00–4.91 (m, 1H), 4.51–4.49 (m, 2H), 4.37 (q, *J* = 7 Hz, 1H), 4.01–3881 (m, 4H), 3.19 (brs, 1H), 1.28–1.24 (m, 3H), 1.10–1.03 (m, 6H), 0.82–0.75 (m, 1H), 0.52–0.47 (m, 1H), 0.42–0.37 (m, 1H), 0.28–0.23 (m, 1H) ppm; ^{13}C{^{1}H} NMR (125 MHz, Acetone-d_6): δ 195.6, 182.0, 156.9, 156.4, 137.6, 127.9, 92.4, 74.7,

69.7, 69.5, 66.4, 61.3, 60.4, 45.1, 27.1, 17.0, 14.1, 14.0, 13.9, 9.2 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{19}H_{26}N_2NaO_7$: 417.1632; found: 417.1639.

The remaining reactions were performed following this general procedure.

Diethyl 1-((4*R*,7*S*)-7-(2-methoxy-4-oxo-4,5-dihydrofuran-3-yl) spiro[2.4]hept-5-en-4-yl) hydrazine-1,2-dicarboxylate (**5b**): Pale brown viscous liquid (107 mg, 76%); ^{1}H NMR (500 MHz, Acetone-d_6, TMS): δ 9.21 (brs, 0.47H), 5.75–5.57 (m, 2H), 5.00–4.90 (m, 1H), 4.52–4.50(m, 2H), 3.99–3.90 (m, 7H), 3.19–3.18 (m, 1H), 1.10–1.03 (m, 6H), 0.81–0.77 (m, 1H), 0.54–0.47 (m, 1H), 0.41–0.36 (m, 1H), 0.30–0.22 (m, 1H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, Acetone-d_6): δ 195.5, 182.2, 156.9, 156.5, 137.5, 127.9, 92.3, 74.7, 69.7, 61.2, 60.5, 56.3, 45.0, 27.1, 17.0, 14.1, 14.0, 9.2 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{18}H_{24}N_2NaO_7$: 403.1476; found: 403.1472.

Diisopropyl 1-((4*R*,7*S*)-7-(2-ethoxy-4-oxo-4,5-dihydrofuran-3-yl) spiro[2.4]hept-5-en-4-yl)hydrazine-1,2-dicarboxylate (**5c**): pale yellow viscous liquid (111 mg, 75%); FTIR (ν_{max} in cm^{-1}): 3336, 2976, 2930, 1718, 1457, 1393, 1379, 1318, 1248, 1156, 1050, 1026, 849, 773. ^{1}H NMR (500 MHz, Acetone-d_6, TMS): δ 9.04 (brs, 0.50H), 5.75–5.68 (m, 1H), 5.58–5.57 (m, 1H), 5.00–4.88 (m, 1H), 4.78–4.64 (m, 3H), 4.50–4.80 (m, 2H), 4.37 (q, *J* = 7.0 Hz, 2H), 3.19 (brs, 1H), 1.27–1.25 (m, 3H), 1.12–1.03 (m, 12H), 0.81–0.73 (m, 1H), 0.51–0.46 (m, 1H), 0.42–0.38 (m, 1H), 0.27–0.22 (m, 1H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, Acetone-d_6): δ 186.1, 172.4, 157.0, 128.4, 128.3, 128.1, 126.7, 100.7, 70.8, 65.9, 60.8, 31.7, 30.8, 27.2, 24.8, 22.4, 21.3, 13.9, 13.4 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{21}H_{30}N_2NaO_7$: 445.1945; found: 445.1951.

Di-*tert*-butyl 1-((4*R*,7*S*)-7-(2-ethoxy-4-oxo-4,5-dihydrofuran-3-yl) spiro[2.4]hept-5-en-4-yl)hydrazine-1,2-dicarboxylate (**5d**): pale yellow viscous liquid (111 mg, 65%); FTIR (ν_{max} in cm^{-1}): 3296, 2983, 2941, 1712, 1573, 1446, 1382, 1301, 1242, 1179, 1115, 1045, 70, 866, 790, 766. ^{1}H NMR (500 MHz, Acetone-d_6, TMS): δ 8.80 (brs, 0.33H), 5.73–5.53 (m, 2H), 4.98–4.83 (m, 1H), 4.54–4.45 (m, 2H), 4.37 (m, 2H), 3.19 (brs, 1H), 1.34–1.24(m, 18H), 1.05 (brs, 3H), 0.79–0.76 (m, 1H), 0.50–0.40 (m, 2H), 0.30–0.18 (m, 1H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, Acetone-d_6): δ 178.8, 174.5, 174.1, 156.1, 155.8, 136.0, 131.0, 100.1, 79.7, 66.2, 61.2, 57.0, 45.7, 38.2, 27.6, 27.4, 26.6, 17.7, 13.6, 9.2 ppm. HRMS (ESI-Orbitrap) m/z: $(M + H)^+$ calcd for $C_{23}H_{34}N_2NaO_7$: 473.2258; found: 473.2269.

Diethyl 1-((4*R*,7*S*)-7-(2-ethoxy-5-methyl-4-oxo-4,5-dihydrofuran-3-yl)spiro[2.4]hept-5-en-4-yl)hydrazine-1,2-dicarboxylate (**5e**): pale yellow viscous liquid (80 mg, 52%); ^{1}H NMR (500 MHz, Acetone-d_6, TMS): δ 9.22–9.18 (m, 0.66H), 5.75–5.53 (m, 2H), 4.99–4.87 (m, 1H), 4.60 (m, 1H), 3.99–3.91 (m, 7H), 3.17 (brs, 1H), 1.31–1.28 (m, 3H), 1.17–1.16 (m, 3H), 1.10–1.03 (m, 6H), 0.79–0.74 (m, 1H), 0.52–0.49 (m, 1H), 0.42–0.36 (m, 1H), 0.29–0.15 (m, 1H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, Acetone-d_6): δ 197.9, 181.0, 156.8, 156.4, 137.7, 127.9, 127.8, 91.0, 83.0, 82.9, 69.7, 61.2, 60.4, 56.4, 45.0, 27.1, 17.2, 16.0, 15.9, 14.1, 14.0, 13.9, 9.2 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{20}H_{28}N_2NaO_7$: 431.1789; found: 431.1784.

Diisopropyl 1-((4*R*,7*S*)-7-(2-ethoxy-5-methyl-4-oxo-4,5-dihydrofuran-3-yl)spiro[2.4]hept-5-en-4-yl)hydrazine-1,2-dicarboxylate (**5f**): pale yellow viscous liquid (70 mg, 45%); ^{1}H NMR (500 MHz, Acetone-d_6, TMS): δ 9.15–9.10 (m, 0.54H), 5.72–5.57 (m, 2H), 5.00–4.87 (m, 1H), 4.71–4.66 (m, 2H), 4.59–4.57 (m, 1H), 4.36 (m, 2H), 3.18 (brs, 1H), 1.30–1.23 (m, 6H), 1.12–1.01 (m, 12H), 0.79–0.70 (m, 1H), 0.50–0.46 (m, 1H), 0.44–0.34 (m, 1H), 0.30–0.14 (m, 1H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, Acetone-d_6): δ 198.0, 180.6, 156.3, 156.0, 137.5, 128.0, 91.0, 82.8, 82.7, 69.6, 68.5, 67.8, 66.2, 44.8, 36.4, 27.2, 21.4, 21.3, 16.9, 16.1, 14.0, 9.1 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{22}H_{32}N_2NaO_7$: 459.2102; found: 459.2109

Experimental procedure for the synthesis of amine-functionalized 3-(2*H*)-furanone-appended hydrazino cyclopentenes: A mixture of 3-(2*H*)-furanone-appended hydrazino cyclopentene (1.0 equiv.,) and amine (1.1 equiv) was weighed into a dry Schlenk tube. Dry methanol (0.2 mM) was added, and the reaction mixture was stirred at 40 °C. Upon completion of the reaction, the solvent was removed, and the residue was subjected to column chromatography on neutral alumina using hexanes/ethyl acetate mixture as eluent to afford the amine-functionalized 3-(2*H*)-furanone appended hydrazino cyclopentene.

Synthesis and characterization of amine-functionalized 3-(2*H*)-furanone-appended hydrazino cyclopentenes:

Dibenzyl 1-((1*S*,4*R*)-4-(2-(hexylamino)-4-oxo-4,5-dihydrofuran-3-yl) cyclopent-2-en-1-yl) hydrazine-1,2-dicarboxylate (**7a**): Following the general experimental procedure, 3-(2*H*)-furanone-appended hydrazino cyclopentene **3h** (50 mg, 0.10 mmol) and n-hexyl amine **6a** (11.3 mg, 0.11 mmol) was weighed into a dry Schlenk tube. Dry methanol (0.5 mL) was added, and the reaction mixture was stirred at 40 °C for 12h. Upon completion of the reaction, the solvent was removed, and the residue was subjected to column chromatography on neutral alumina using hexanes/ethyl acetate mixture as eluent (60% ethyl acetate in hexanes) to afford the desired product **7a** as pale-yellow viscous liquid (54 mg, 98%). Analytical data of **7a**: FTIR (ν_{max} in cm^{-1}): 3463, 3284, 2983, 2948, 1712, 1545, 1510, 1452, 1400, 1254, 1214, 1109, 1045, 744, 692, 587, 506. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.24–7.19 (m, 10H), 5.81 (brs, 1H), 5.59 (brs, 1H), 5.06–5.04 (m, 4H), 4.87 (brs, 1H), 4.36 (s, 2H), 3.65 (brs, 1H), 3.20–3.12 (m, 2H), 2.58 (brs, 1H), 1.77 (brs, 1H), 1.45–1.53 (m, 2H), 1.21–1.18 (m, 6H), 0.80 (t, *J* = 6.5Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 191.4, 177.5, 156.7, 155.4, 135.8, 130.9, 128.6, 128.4, 128.2, 128.1, 127.7, 93.4, 74.1, 67.9, 67.7, 41.5, 35.8, 31.3, 29.9, 26.9, 26.3, 22.5, 14.0 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{31}H_{37}N_3NaO_6$: 570.2575; found: 570.2579.

The remaining reactions were performed following this general procedure:

Dibenzyl 1-((1*S*,4*R*)-4-(2-(benzylamino)-4-oxo-4,5-dihydrofuran-3-yl)cyclopent-2-en-1-yl)hydrazine-1,2-dicarboxylate (**7b**): Pale yellow viscous liquid (52 mg, 92%); FTIR (ν_{max} in cm^{-1}): 3463, 3259, 3069, 3040, 2948, 1706, 1556, 1499, 1463, 1417, 1208, 1057, 1005, 750, 611, 576, 495. ^{1}H NMR (500 MHz, CD_3CN, TMS): δ 7.25–7.20 (m, 15H), 5.61–5.53 (m, 2H), 5.14–4.95 (m, 5H), 4.39–4.38 (m, 2H), 4.21 (brs, 2H), 3.35 (brs, 1H), 2.46–2.43 (m, 1H), 1.84 (brs, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, CD_3CN): δ 192.6, 178.1, 157.5, 156.1, 137.3, 129.2, 129.0, 128.5, 128.1, 128.0, 127.8, 93.0, 74.6, 67.8, 66.9, 65.6, 45.0, 37.4, 33.1 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{32}H_{31}N_3NaO_6$: 576.2105; found: 576.2118.

Dibenzyl-1-((1*S*,4*R*)-4-(2-((2-bromobenzyl)amino)-4-oxo-4,5-dihydrofuran-3-yl)cyclopent-2-en-1-yl)hydrazine-1,2-dicarboxylate (**7c**): Pale yellow viscous liquid (46 mg, 72%); FTIR (ν_{max} in cm^{-1}): 3492, 3267, 2983, 2924, 2885, 1719, 1596, 1336, 1242, 1057, 1028, 756, 675, 582. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.49 (d, *J* = 8Hz, 1H), 7.25–7.11 (m, 13H), 5.66–5.58 (m, 2H), 5.14–4.94 (m, 5H), 4.45 (s, 2H), 4.21 (s, 2H), 3.41 (brs, 1H), 2.52–2.45 (m, 1H), 1.85 (brs, 1H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 192.1, 177.4, 156.6, 155.4, 136.8, 135.8, 135.7, 132.9, 131.1, 129.2, 128.9, 128.5, 128.4, 128.2, 128.1, 127.8, 127.7, 122.9, 94.2, 74.2, 67.9, 67.7, 45.3, 35.7 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{32}H_{30}N_3NaO_6Br$: 654.1210; found: 654.1195.

Diethyl-1-((4*R*,7*S*)-7-(2-((2-bromobenzyl)amino)-4-oxo-4,5-dihydrofuran-3-yl)spiro[2.4]hept-5-en-4-yl)hydrazine-1,2-dicarboxylate (**7d**): Pale yellow viscous liquid (35 mg, 50%); ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.50 (d, *J* = 7.5 Hz, 1H), 7.25 (t, *J* = 7.0 Hz, 2H), 7.11 (t, *J* = 7Hz, 1H), 5.94–5.82 (m, 2H), 4.58–4.50 (m, 2H), 4.45–4.35 (m, 3H), 4.17–4.00 (m, 4H), 3.73 (brs, 1H), 1.18–1.12 (m, 7H), 0.81–0.79 (m, 2H), 0.44–0.37 (m, 1H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 192.2, 177.8, 177.5, 157.3, 136.9, 133.5, 131.0, 129.4, 128.4, 127.8, 123.1, 74.3, 62.4, 45.4, 43.2, 29.7, 14.3, 10.5 ppm. HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{24}H_{28}N_3NaO_6Br$:556.1054; found: 556.1059.

Experimental procedure for the intramolecular Heck reaction of amine-functionalized 3-(2*H*)-furanone-appended hydrazino cyclopentenes: A mixture of amine-functionalized 3-(2H)-furanone-appended hydrazino cyclopentenes (1.0 equiv.), $Pd(OAc)_2$ (5 mol%), P(*o*-tol)$_3$ (10 mol%) and Et_3N (1.0 equiv.) was weighed in a Schlenk tube and degassed for 10 min. Dry ACN (0.025 mM) was added and the reaction mixture was purged with argon and allowed to stir at 100 °C for 12h. The solvent was evaporated in vacuo and the residue on silica gel (100–200 mesh) column chromatography yielded compound 8.

Following the general experimental procedure, Dibenzyl-1-((1*S*,4*R*)-4-(2-((2-bromobenzyl) amino)-4-oxo-4,5-dihydrofuran-3-yl)cyclopent-2-en-1-yl)hydrazine-1,2-dicarboxylate **7c** (32 mg, 0.0506 mmol) $Pd(OAc)_2$ (0.51 mg, 0.0025 mmol), P(*o*-tol)$_3$ (1.6 mg, 0.0051 mmol) and Et_3N (5.1 mg, 0.0506 mmol) was weighed in a Schlenk tube and degassed for 10 min. Dry ACN (2 mL) was added and the reaction mixture was purged with argon and allowed

to stir at 100 °C for 12h. Upon completion of the reaction, the solvent was removed, and the residue was subjected to column chromatography on silica gel (100–200 mesh) using hexanes/ethyl acetate mixture as eluent (70% ethyl acetate in hexanes) to afford the **8c** as pale-yellow viscous liquid (18 mg, 65%). Analytical data was the same as **7b**.

4. Conclusions

We have developed a methodology for the ring-opening of diazabicyclic olefins via a Pd-catalyzed reaction with 4-halo-1,3-dicarbonyl compounds. This reaction has resulted in the generation of a new class of 3(2*H*)-furanone-appended hydrazino cyclopentenes. This ring opening reaction of diazabicyclic olefins was found to be general with different 4-halo-1,3-dicarbonyl compounds and we could also synthesize another interesting scaffold, namely, 3(2*H*)-furanone-substituted spiro[2.4]hept-5-ene from cyclopropane-appended spirotricyclic olefin. We have proposed a mechanism which proceeds via the formation of a π-allylpalladium intermediate, which is quenched by the active methylene moiety generated from 4-halo1,3-dicarbonyl moiety, and an intramolecular cyclization in the intermediate then generates the product. We then utilized the synthesized 3(2*H*)-furanone-appended hydrazino cyclopentenes for the generation of amine-functionalized 3-(2H)-furanone-appended hydrazino cyclopentenes. Finally, we tried to generate a new family of 3(2*H*)-furanone-fused tetrahydroazocine derivatives which did not result in the expected outcome.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/org4010006/s1, Table S1: Optimization studies for intramolecular Heck coupling; Figure S1: 1H NMR and 13C NMR Spectra of 3a; Figure S2: 1H-1H COSY Spectrum of 3a; Figure S3: HMQC Spectrum of 3a; Figure S4: HMBC Spectrum of 3a; Figure S5: 1D-NOE Spectrum of 3a; Figure S6: 1H NMR (500 MHz) & 13C (125 MHz) Spectra of 3b; Figure S7: 1H NMR (500 MHz) & 13C (125 MHz) Spectra of 3c; Figure S8: 1H NMR (500 MHz) & 13C (125 MHz) Spectra of 3d; Figure S9: 1H NMR (500 MHz) & 13C (125 MHz) Spectra of 3e; Figure S10: 1H NMR (500 MHz) & 13C (125 MHz) Spectra of 3f; Figure S11: 1H NMR (500 MHz) & 13C (125 MHz) Spectra of 3g; Figure S12: 1H NMR (500 MHz) & 13C (125 MHz) Spectra of 3h; Figure S13: 1H NMR (500 MHz) & 13C (125 MHz) Spectra of 3i; Figure S14: 1H NMR (500 MHz) & 13C (125 MHz) Spectra of 3j; Figure S15: 1H NMR (500 MHz) & 13C (125 MHz) spectra of 3k; Figure S16: 1H NMR (500 MHz) & 13C (125 MHz) Spectra of 5a; Figure S17: 1H NMR (500 MHz) & 13C (125 MHz) Spectra of 5b; Figure S18: 1H NMR (500 MHz) & 13C (125 MHz) Spectra of 5c; Figure S19: 1H NMR (500 MHz) & 13C (125 MHz) Spectra of 5d; Figure S20: 1H NMR (500 MHz) & 13C (125 MHz) Spectra of 5e; Figure S21: 1H NMR (500 MHz) & 13C (125 MHz) Spectra of 5f; Figure S22: 1H NMR (500 MHz) & 13C (125 MHz) Spectra of 7a; Figure S23: 1H NMR (500 MHz) & 13C (125 MHz) Spectra of 7b; Figure S24: 1H NMR (500 MHz) & 13C (125 MHz) Spectra of 7c; Figure S25: 1H NMR (500 MHz) & 13C (125 MHz) Spectra of 7d.

Author Contributions: Conceptualization, J.J.; methodology, J.J., V.K.O. and A.V.; validation, J.J. and V.K.O.; formal analysis, J.J. and V.K.O. investigation J.J., V.K.O. and A.V. writing—original draft preparation, J.J. and V.K.O. writing—review and editing, J.J. and H.H. supervision, J.J.; project administration, J.J.; funding acquisition, J.J. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: All data supporting the reported results can be found in the Supporting Information file.

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References

1. Colin Slaughter, J.C. The naturally occurring furanones: Formation and function from pheromone to food. *Biol. Rev.* **1999**, *74*, 259. [CrossRef] [PubMed]
2. Carter, N.B.; Nadanya, A.E.; Sweeney, J.B. Recent developments in the synthesis of furan-2(5*H*)-ones. *J. Chem. Soc. Perkin Trans. 1.* **2002**, 2324. [CrossRef]
3. de Nys, R.; Givskov, M.; Kumar, N.; Kjelleberg, S.; Steinberg, P.D. *Marine Molecular Biotechnology*; Fusetani, N., Clare, A.S., Eds.; Springer: Berlin/Heidelberg, Germany, 2006; Volume 42.
4. Schwab, W. Natural 4-Hydroxy-2,5-dimethyl-3(2*H*)-furanone. *Molecules* **2013**, *18*, 6936. [CrossRef]
5. Husain, A.; Khan, S.A.; Iram, F.; Iqbal, M.A.; Asif, M. Insights into the chemistry and therapeutic potential of furanones: A versatile pharmacophore. *Eur. J. Med. Chem.* **2019**, *171*, 66. [CrossRef] [PubMed]
6. Smith, A.B., III; Levenberg, P.A.; Jerris, P.J.; Scarborough, R.M., Jr.; Wovkulich, P.M. Synthesis and reactions of simple 3(2*H*)-furanones. *J. Am. Chem. Soc.* **1981**, *103*, 1501. [CrossRef]
7. Jerris, P.J.; Smith, A.B., III. Synthesis and configurational assignment of geiparvarin: A novel antitumor agent. *J. Org. Chem.* **1981**, *46*, 577. [CrossRef]
8. Marson, C.M.; Edaan, E.; Morrell, J.M.; Coles, S.J.; Hursthouse, M.B.; Davies, D.T. A catalytic asymmetric protocol for the enantioselective synthesis of 3(2*H*)-furanones. *Chem. Commun.* **2007**, 2494. [CrossRef] [PubMed]
9. Haug, T.T.; Kirsch, S.F. Synthesis and chemistry of 3(2*H*)-furanones. *Targets Heterocycl. Syst.* **2009**, *13*, 57.
10. Omanakuttan, V.K.; John, J.; Hopf, H. Synthesis of 3(2*H*)-furanones-a review. *Eur. J. Org. Chem.* **2021**, *2021*, 163. [CrossRef]
11. Dou, X.; Han, X.; Lu, Y. From the Feist–Bénary Reaction to Organocatalytic Domino Michael–Alkylation Reactions: Asymmetric Synthesis of 3(2*H*)-Furanones. *Chem. Eur. J.* **2012**, *18*, 85. [CrossRef]
12. Yan, Y.-Y.; Lu, R.-J.; Wang, J.-J.; Xuan, Y.-N.; Yan, M. Synthesis of chiral tetronic acid derivatives via organocatalytic conjugate addition of ethyl 4-chloro-3-oxobutanoate to nitroalkenes. *Tetrahedron* **2012**, *68*, 6123. [CrossRef]
13. Zhou, J.; Bai, L.; Liang, G.; Chen, Y.; Gan, Z.; Wang, W.; Zhou, H.; Yu, Y. Organocatalytic asymmetric domino Michael/O-alkylation reaction for the construction of succinimide substituted 3(2*H*)-furanones catalyzed by quinine. *RSC Adv.* **2017**, *7*, 39885. [CrossRef]
14. John, J.; Hopf, H. Substituted 3(2*H*)-Furanones by a Tandem Michael Addition/Palladium-Catalyzed Ring-Closing Protocol. *Eur. J. Org. Chem.* **2013**, *2013*, 841. [CrossRef]
15. John, J.; Târcoveanu, E.; Jones, P.G.; Hopf, H. A tandem Mannich addition–palladium catalyzed ring-closing route toward 4-substituted-3-(2*H*)-furanones. *Beilstein J. Org. Chem.* **2014**, *10*, 1462. [CrossRef] [PubMed]
16. John, J.; Omanakuttan, V.K.; Aneeja, T.; Suresh, C.H.; Jones, P.G.; Hopf, H. Tandem α-Arylation/Cyclization of 4-Haloacetoacetates with Arynes: A Metal-Free Approach toward 4-Aryl-3-(2*H*)-furanones. *J. Org. Chem.* **2019**, *84*, 5957. [CrossRef]
17. Omanakuttan, V.K.; Santhini, P.V.; Shaludheen, S.; Varughese, S.; Hopf, H.; John, J. Tandem Reaction of 4-Halo-1,3-Dicarbonyl Compounds with Alkynes towards 4-Vinyl-3(2*H*)-Furanones and 3(2*H*)-Furanone fused 2-Pyridones. *Asian J. Org. Chem.* **2022**, *11*, e202200410. [CrossRef]
18. Bournaud, C.; Chung, F.; Luna, A.; Pasco, M.; Errasti, G.; Lecourt, T.; Micouin, L. Stereoselective Transformations of meso Bicyclic Hydrazines: Versatile Access to Functionalized Aminocyclopentanes. *Synthesis* **2009**, *2009*, 869. [CrossRef]
19. Sajisha, S.; Anas, S.; John, J.; Radhakrishnan, K.V. Desymmetrization of meso-Bicyclic Hydrazines: An Efficient Strategy towards the Synthesis of Functionalized Cyclopentenes. *Synlett* **2009**, *2009*, 2885. [CrossRef]
20. Pineschi, M. The Binomial Copper-Catalysis and Asymmetric Ring Opening of Strained Heterocycles: Past and Future Challenges. *Eur. J. Org. Chem.* **2020**, *2020*, 2643. [CrossRef]
21. Preethalayam, P.; Jijy, E.; Prakash, P.; Sarngadharan, S.C.; Vijayan, A.; Radhakrishnan, K.V.; John, J. Diazanorbornene: A Valuable Synthon towards Carbocycles and Heterocycles. *Eur. J. Org. Chem.* **2020**, *2020*, 6588. [CrossRef]
22. Allred, E.L.; Anderson, C.L.; Smith, R.L. Hydroboration of 2,3-dicarbomethoxy-2,3-diazabicyclo [2.2.1]hept-5-ene. The elimination mechanism of the organoborane intermediate. *Tetrahedron Lett.* **1966**, *9*, 951. [CrossRef]
23. Wilson, R.M.; Schnapp, K.A.; Merwin, R.K.; Ranganathan, R.; Moats, D.L.; Conrad, T.T. Synthesis of allylic alcohol single-chain PGH analogs. A synthetic application of the argon laser. *J. Org. Chem.* **1986**, *51*, 4028. [CrossRef]
24. Bournaud, C.; Lecourt, T.; Micouin, L.; Méliet, C.; Agbossou-Niedercorn, F. Desymmetrization of meso-Bicyclic Hydrazines by Rhodium-Catalyzed Enantioselective Hydroformylation. *Eur. J. Org. Chem.* **2008**, *2008*, 2298. [CrossRef]
25. Mellor, J.M.; Smith, N.M. Reductive cleavage of the nitrogen–nitrogen bond in hydrazine derivatives. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2927–2931. [CrossRef]
26. Grabowski, S.; Armbruster, J.; Prinzbach, H. Biocatalysis in the chiral recognition of meso-diamides—An efficient route from cyclic olefinic hydrocarbons to optically pure diamino-polyols. *Tetrahedron Lett.* **1997**, *38*, 5485. [CrossRef]
27. Storsberg, J.; Nandakumar, M.V.; Sankaranarayanan, S.; Kaufmann, D.E. Stereoselective Palladium-Catalyzed C-C Coupling Reactions with a Diazabicyclo [2.2.1]heptane. *Adv. Synth. Catal.* **2001**, *343*, 177. [CrossRef]
28. Yao, M.-L.; Adiwidjaja, G.; Kaufmann, D.E. Two-Step, Stereoselective Hydrazidoarylation of 1,3-Cyclopentadiene. *Angew. Chem. Int. Ed.* **2002**, *41*, 3375. [CrossRef]

29. Radhakrishnan, K.V.; Sajisha, V.S.; Anas, S.; Krishnan, K.S. Palladium-Catalyzed Reaction of Bicyclic Hydrazines with Allyl- and Arylstannanes in Ionic Liquid [bmim]PF6: A Facile Method for the Synthesis of Substituted Hydrazinocyclopentene Derivatives. *Synlett* **2005**, *2005*, 2273. [CrossRef]
30. Sajisha, V.S.; Mohanlal, S.; Anas, S.; Radhakrishnan, K.V. A facile synthesis of 3-allyl-4-hydrazinocyclopentenes by the palladium/Lewis acid mediated ring opening of bicyclic hydrazines with allyltributyltin and allyltrimethylsilane. *Tetrahedron* **2006**, *62*, 3997. [CrossRef]
31. Sajisha, V.S.; Radhakrishnan, K.V. Palladium/Lewis Acid-Catalyzed Reactions of Bicyclic Hydrazines with Organostannanes: A General Methodology for the Stereoselective Synthesis of 3,4-Disubstituted Cyclopentenes. *Adv. Synth. Catal.* **2006**, *348*, 924. [CrossRef]
32. John, J.; Sajisha, V.S.; Mohanlal, S.; Radhakrishnan, K.V. Iodine assisted modified Suzuki type reaction of bicyclic hydrazines: Stereoselective synthesis of functionalized cyclopentene. *Chem. Commun.* **2006**, 3510–3512. [CrossRef]
33. Bournaud, C.; Falciola, C.; Lecourt, T.; Rosset, S.; Alexakis, A.; Micouin, L. On the Use of Phosphoramidite Ligands in Copper-Catalyzed Asymmetric Transformations with Trialkylaluminum Reagents. *Org. Lett.* **2006**, *8*, 3581. [CrossRef] [PubMed]
34. Anas, S.; John, J.; Sajisha, V.S.; Rajan, R.; Suresh, E.; Radhakrishnan, K.V. Iodine assisted palladium catalyzed ring opening of bicyclic hydrazines with organoboronic acids: Stereoselective synthesis of functionalized cyclopentenes and alkylidene cyclopentenes. *Org. Biomol. Chem.* **2007**, *5*, 4010. [CrossRef]
35. John, J.; Anas, S.; Sajisha, V.S.; Viji, S.; Radhakrishnan, K.V. Palladium-catalyzed ring opening of azabicyclic olefins with organoindium reagents: A simple, clean, and efficient synthesis of functionalized cyclopentenes. *Tetrahedron Lett.* **2007**, *48*, 7225. [CrossRef]
36. John, J.; Adarsh, B.; Radhakrishnan, K.V. Palladium catalyzed ring opening of azabicyclic olefins with organoindium and gallium reagents: A facile access towards benzylated cyclopentanoids. *Tetrahedron* **2010**, *66*, 1383. [CrossRef]
37. Joseph, N.; Rajan, R.; John, J.; Devika, N.V.; Chand, S.S.; Suresh, E.; Pihko, P.M.; Radhakrishnan, K.V. An exclusive approach to 3,4-disubstituted cyclopentenes and alkylidene cyclopentenes via the palladium catalyzed ring opening of azabicyclic olefins with aryl halides. *RSC Adv.* **2013**, *3*, 7751. [CrossRef]
38. John, J.; Indu, U.; Suresh, E.; Radhakrishnan, K.V. Palladium Catalyzed Tandem Ring Opening−Ring Closing Reaction of Diazabicyclic Alkenes: A Facile One Pot Strategy for Cyclopentannulation of Heterocycles. *J. Am. Chem. Soc.* **2009**, *131*, 5042. [CrossRef] [PubMed]
39. John, J.; Rajan, R.; Chand, S.S.; Prakash, P.; Joseph, N.; Suresh, E.; Radhakrishnan, K.V. Palladium catalyzed reaction of ortho-functionalized aryl iodides with bicyclic hydrazines: Facile route toward heteroannulated cyclopentenes and azabicycles. *Tetrahedron* **2013**, *69*, 152. [CrossRef]
40. Jijy, E.; Prakash, P.; Shimi, M.; Pihko, P.M.; Joseph, N.; Radhakrishnan, K.V. Rhodium catalyzed oxidative coupling of salicylaldehydes with diazabicyclic olefins: A one pot strategy involving aldehyde C–H cleavage and π-allyl chemistry towards the synthesis of fused ring chromanones. *Chem. Commun.* **2013**, *49*, 7349. [CrossRef]
41. Santhini, P.V.; Nimisha, G.; John, J.; Suresh, E.; Varma, R.L.; Radhakrishnan, K.V. Pd-Catalyzed oxidative annulation of enamides with diazabicyclic olefins: Rapid access to cyclopentene fused 2-pyrrolines. *Chem. Commun.* **2017**, *53*, 1848. [CrossRef]
42. Santhini, P.V.; Smrithy, A.S.; Jesin, C.P.I.; Varughese, S.; John, J.; Radhakrishnan, K.V. Accessing highly functionalized cyclopentanoids via a cascade palladation approach: Unprecedented benzylic C–H activation towards cyclopentenoindanes. *Chem. Commun.* **2018**, *54*, 2982. [CrossRef] [PubMed]
43. Luna, A.P.; Cesario, M.; Bonin, M.; Micouin, L. Stereoselective Ring Opening of meso Bicyclic Hydrazines: A Straightforward Approach to Hydrazino Cyclopentenic Cores. *Org. Lett.* **2003**, *5*, 4771. [CrossRef] [PubMed]
44. Rajan, R.; John, J.; Thulasi, S.; Joseph, N.; Radhakrishnan, K.V.; Sawant, R.C. Trapping the π-Allylpalladium Intermediate from Fulvene-Derived Azabicyclic Olefin with Soft Nucleophiles. *Synthesis* **2010**, *2010*, 3649. [CrossRef]
45. Jijy, E.; Prakash, P.; Baiju, V.; Shimi, M.; Yamamoto, Y.; Suresh, E.; Radhakrishnan, K.V. Palladium-Catalyzed Ring Opening of Cyclopropane-Appended Spirotricyclic Olefins with Soft Nucleophiles and Organoboronic Acids: Facile Synthesis of Functionalized Spiro [2.4]heptenes. *Synthesis* **2014**, *46*, 2629. [CrossRef]
46. Negishi, E. *Hand Book of Organopalladium Chemistry for Organic Synthesis*; Wiley-Interscience: New York, NY, USA, 2002; Volume 2.
47. Pashkovskii, F.S.; Shchukina, E.M.; Gribovskii, M.G.; Lakhvich, F.A. Heterocyclic Analogs of Prostaglandins: III. Synthesis of 10-Oxa-13-Aza, 11-Oxa-13-Aza, and 9-Oxa-7-Aza Prostanoids from 3-Acyl-and 3-(3-Arylprop-2-enoyl)Furan-2,4-Diones. *Russ. J. Org. Chem.* **2006**, *42*, 527. [CrossRef]
48. Sutharchanadevi, M.; Murugan, R. *9.18—Eight-membered Rings with One Nitrogen Atom*; Katritzky, A.R., Rees, C.W., Scriven, E.F.V., Eds.; Comprehensive Heterocyclic Chemistry II: Pergamon, Turkey, 1996; pp. 403–428.
49. Listratova, A.V.; Voskressensky, L.G. Recent Advances in the Synthesis of Hydrogenated Azocine-Containing Molecules. *Synthesis* **2017**, *49*, 3801.
50. Mack, R.A.; Zazulak, W.I.; Radov, L.A.; Baer, J.E.; Stewart, J.D.; Elzer, P.H. Drug-induced modifications of the immune response. 12. 4,5-Dihydro-4-oxo-2-(substituted amino)-3-furancarboxylic acids and derivatives as novel antiallergic agents. *J. Med. Chem.* **1988**, *31*, 1918. [CrossRef]
51. Choi, H.Y.; Chi, D.Y. Nonselective bromination-selective debromination strategy: Selective bromination of unsymmetrical ketones on singly activated carbon against doubly activated carbon. *Org. Lett.* **2003**, *5*, 411. [CrossRef]

52. Takaaki, K.; Katsumasa, H. Preparation of γ-Halogeno-β-keto esters, Japan. Patent Application No. JP1999-56383; Patent No. JP2000256262, 19 September 2000.
53. Hu, D.; Grice, P.; Ley, S.V. Rotamers or diastereomers? *An overlooked NMR solution. J. Org. Chem.* **2012**, *77*, 5198.

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Tandem Reaction of 4-Halo-1,3-Dicarbonyl Compounds with Alkynes towards 4-Vinyl-3(2*H*)-Furanones and 3(2*H*)-Furanone fused 2-Pyridones

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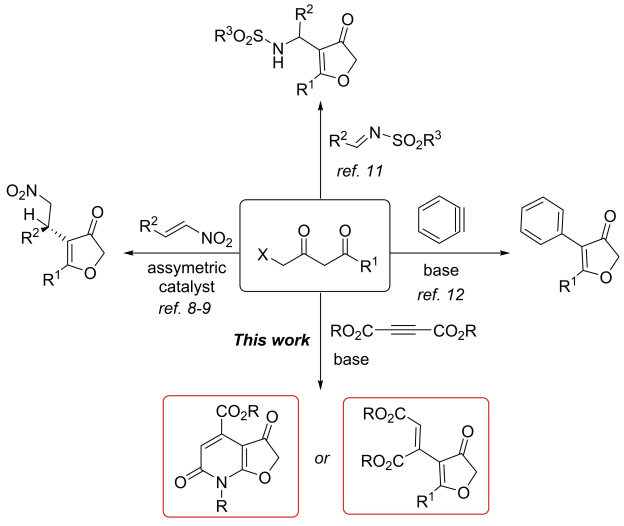
Abstract: A facile synthetic route of 4-vinyl-3(2*H*)-furanones from the reaction of 4-halo-1,3-dicarbonyl compounds and alkynes is reported, a reaction taking place *via* tandem Michael addition and intramolecular cyclization. The formation of a side-product (regioisomer) by a stepwise [2+2] cycloaddition between enolate (of the 4-halo-1,3-dicarbonyl compound) and activated alkyne followed by a sequential 4π-ring opening and an intramolecular cyclization has also been noted. Another interesting observation was the formation of 3(2*H*)-furanone fused 2-pyridone from the reaction of 4-bromo-3-oxo-*N*-alkyl(aryl)butanamide with activated alkynes. All reactions were found to be general affording the corresponding substituted/fused 3(2*H*)-furanones in satisfactory to good yields.

Introduction

Among the class of oxygen-containing heterocycles, furanones hold an important position due to its wide presence in natural products and pharmacophores.[1] Based on the structure and position of functionalities, furanones are divided into three classes (i) 2(3*H*)-furanones, (ii) 2(5*H*)-furanones and (iii) 3(2*H*)-furanones.[2] Amidst these types of furanones present, 3(2*H*)-furanones form an imperative class consisting of simple natural products such as bullatenone to complex ones such as eremantholides.[3] Functionalized 3(2*H*)-furanones were also found to exhibit biological activities including antiulcer, anti-allergic, anti-inflammatory and antitumor activities which has made them compelling research problems for chemists.[4]

Over the past five decades a number of synthetic methodologies were developed towards this class of oxygen-heterocycles.[3,5] Initially, all synthetic methodologies were focused to aid in the total syntheses of 3(2*H*)-furanone containing natural products.[6] Among the reported methods for accessing functionalized 3(2*H*)-furanones there are several acid or base mediated, Lewis acid or base and metal-catalyzed processes, tandem approaches, one-pot methods and enantioselective syntheses.[3,5,7] Recently, it was found that the reaction of 4-haloacetoacetates with electrophiles in the presence of a base or catalyst gives rise to 4,5-disubstituted-3(2*H*)-furanones (Scheme 1). The first report in this line came from the group of Lu and co-workers who introduced an asymmetric synthesis of 4,5-disubstituted-3(2*H*)-furanones *via* a modified Feist-Bénary reaction.[8] At the same time another quinine catalyzed asymmetric synthesis of 4,5-disubstituted-3(2*H*)-furanones from the reaction of 4-haloacetoacetate and nitro olefin came from the group of Yan and co-workers.[9] In 2013, while attempting the synthesis of functionalized cyclopentanes from the Pd-catalyzed reaction of 4-chloroacetoacetate and activated sytrenes, we observed the formation of 4,5-disubstituted-3(2*H*)-furanones.[10] Later, we extended the reaction to other electrophiles such as



Scheme 1. Synthesis of 4-substituted-3(2*H*)-furanones from 4-haloacetoacetate.

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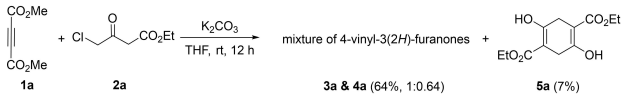
activated imines[11] and arynes.[12] In the present work, we attempted the reaction of 4-haloacetoacetates with activated alkynes yielding 4-vinyl-substituted-3(2*H*)-furanones. By using appropriately functionalized 4-halo-1,3-dicarbonyl compounds, we could synthesize a new class of furanone fused pyridone derivatives.

Results and Discussion

We initiated the investigations with activated alkyne, dimethyl acetylenedicarboxylate **1a** and ethyl-4-chloroacetoacetate **2a** as substrates (Scheme 2). The first reaction of **1a** with **2a** was performed in the presence of 2.0 equivalents of K_2CO_3 in THF at room temperature for 12 hours. From the reaction mixture, we isolated a mixture of 4-vinyl-3-(2*H*)-furanones in 64% yield which we initially thought were stereoisomers. In addition, a dimer of ethyl-4-chloroacetoacetate, **5a** was also isolated in 7% yield. In order to characterize the components of the isolated mixture, we performed an additional column chromatography which took us 3 days to separate between the two. Since we could not get conclusive evidence for the structures of the isolated compounds from NMR and HRMS analyses, we crystallized both products and performed a single crystal X-ray analysis.



Scheme 2. Synthesis of 4-vinyl-3-(2*H*)-furanone from activated alkyne and 4-chloroacetoacate.

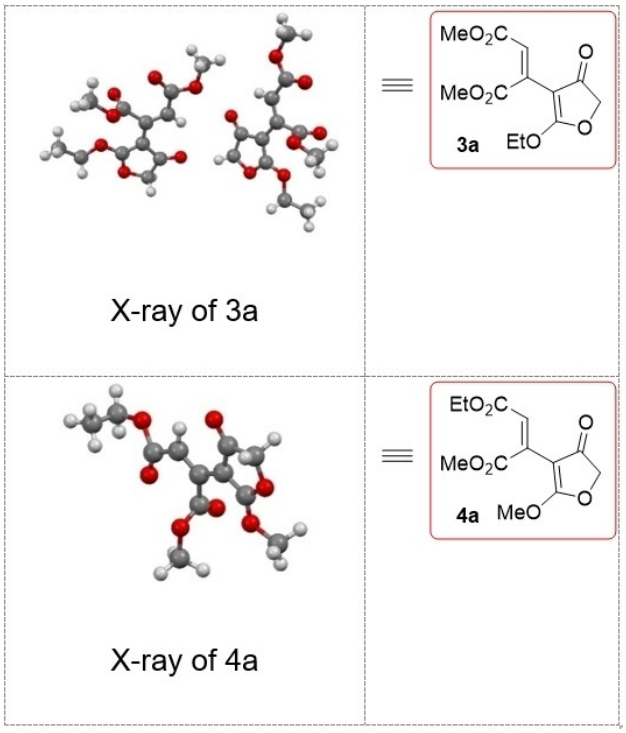


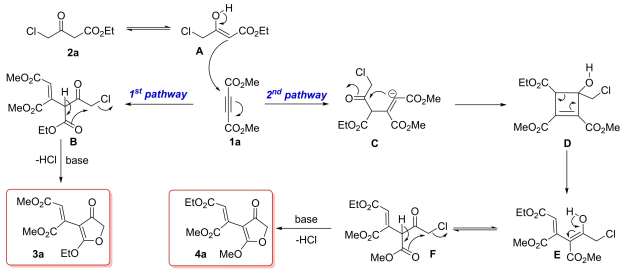
Figure 1. X-ray crystal structures of **3a** and **4a**.

The single crystal X-ray structures of **3a** and **4a** are shown in figure 1. From the crystal data, it is evident that the structure of **3a** was as expected. In the crystal structure of **4a**, we observed that an interchange between the alkyl groups of the ester moieties of **1a** and **2a** had taken place and hence a regioisomer of **3a**.

The possible mechanisms for the formation of both **3a** and the regioisomer **4a** are depicted in scheme 3. Both the pathways start with the Michael addition of **2a** to **1a**. Keto-enol tautomerism is possible in ethyl-4-chloroacetoacate **2a** and the enol form **A** undergoes a Michael addition with the activated alkyne to form **B**. Then, base abstracts the acidic proton in intermediate **B** generating the ester enolate which then attacks (*via* enolate oxygen) the carbon bearing the halogen furnishing the expected 4-vinyl-3-(2*H*)-furanone **3a**. Stepwise [2+2] cycloadditions of enamines and enols to activated alkynes towards cyclobutenes is well explored and the 2nd pathway is proposed based on these literature precedents.[13] The 2nd pathway starts with the attack of the vinylic anionic centre to the carbonyl carbon forming the cyclobutene intermediate **D**. A 4π-ring opening takes place in **D** furnishing the diene **E** which upon tautomerization affords intermediate **F**. Finally, as seen in the previous pathway, base abstracts the acidic proton in intermediate **F** generating the ester enolate which then attacks (*via* enolate oxygen) the carbon bearing the halogen furnishing the unexpected regioisomer 4-vinyl-3-(2*H*)-furanone **4a**.

Our next focus was on finding the best conditions for achieving the highest yield for 4-vinyl-3-(2*H*)-furanones with **1a** and **2a** as model substrates (Table 1).

The optimization studies commenced with the screening of bases such as Na_2CO_3, K_2CO_3, NaOAc, Et_3N, CsOAc and NH_4OAc. (Table1, entries 1–6). Among the screened bases, Na_2CO_3 gave the maximum yield of 82% for the mixture of **3a** and **4a**. Next, we examined different solvents such as THF, CH_3CN, DMF and toluene. From the solvent optimization, our initial choice of THF was found to be the best medium for the present transformation (Table 1, entries 7–9). Increasing the temperature and time of the reaction did not have any marked improvements in the outcome. Thus the optimized conditions for the reaction was found to be a combination of 1.0 equivalent of activated alkyne **1**, 1.1 equivalent of 4-haloacetoacetate **2** and 2.0



Scheme 3. Possible mechanism for the formation of 4-vinyl-3-(2*H*)-furanones **3a** and regioisomer **4a** from activated alkyne **1a** and ethyl-4-chloroacetoacate **2a**.

Table 1. Optimization studies.

1a 2a 3a 4a

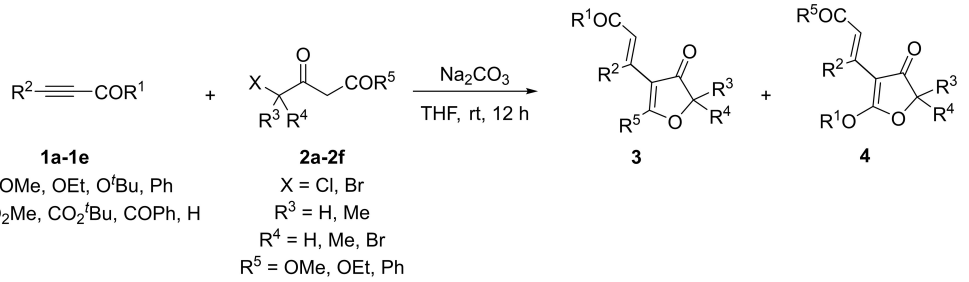
Entry	Base	Solvent	Yield of **3a** & **4a** [%][a]
1	K_2CO_3	THF	64
2	**Na_2CO_3**	**THF**	**82**
3	NaOAc	THF	75
4	Et_3N	THF	44
5	CsOAc	THF	41
6	NH_4OAc	THF	–
7	Na_2CO_3	CH3CN	40
8	Na_2CO_3	Toluene	45
9	Na_2CO_3	DMF	35
10[b]	Na_2CO_3	THF	43
11[c]	Na_2CO_3	THF	80

Reaction conditions: [a] **1a** (1.0 equiv., 0.70 mmol), **2a** (1.1 equiv., 0.78 mmol), base (2.0 equiv.), solvent (4.0 mL), rt, 12 h, isolated yield; [b] 50 °C; [c] 24 h.

equivalents of Na_2CO_3 as base in THF at room temperature for 12 h. In all cases, we isolated the mixture of **3a** and **4a**.

These optimized conditions for the tandem Michael Addition/Intramolecular cyclisation strategy were initially utilized for studying the generality of differently substituted activated alkynes (Table 2). The reaction of dimethyl acetylenedicarboxylate **1a** and ethyl-4-chloroacetoacetate **2a** under the optimized condition afforded a 1:0.69 mixture of 4-vinyl-3(2*H*)-furanones **3a** and the regioisomer **4a** in 82% yield. In a similar fashion, di-*tert*-butyl acetylenedicarboxylate **1b** also reacted with **2a** furnishing a 1:0.62 regioisomeric mixture of 4-vinyl-3(2*H*)-furanones **3b** and **4b** in 39% yield. The reaction of 1,4-diphenylbut-2-yne-1,4-dione **1c** with methyl-4-chloroacetoacetate **2f** furnished only the 4-vinyl-3(2*H*)-furanones **3c** due to the presence of the keto-group instead of the ester moiety thereby preventing the 2nd pathway towards the stepwise [2+2] cycloaddition and subsequent electrocyclic 4π-ring opening. The reactions of 4-bromo-1-phenylbutane-1,3-dione **2b** and 4,4-dibromo-1-phenylbutane-1,3-dione **2c** with dimethylacetylene dicarboxylate **1a** also resulted in 4-vinyl-3(2*H*)-furanones **3d** and **3e** (Table 2). It is noteworthy to mention that in **3e** (despite of the poor yield), a bromine functionality could be placed at the 2nd position by starting from 2,4-dibromo-1-phenylbutane-1,3-dione **2c**. The same strategy was adopted for introducing methyl substituents at the 2nd position of 3(2*H*)-furanone ring by carrying out reactions of ethyl 4-bromo-3-oxopentanoate **2d** and ethyl 4-bromo-4-methyl-3-oxopentanoate **2e** with dimeth-

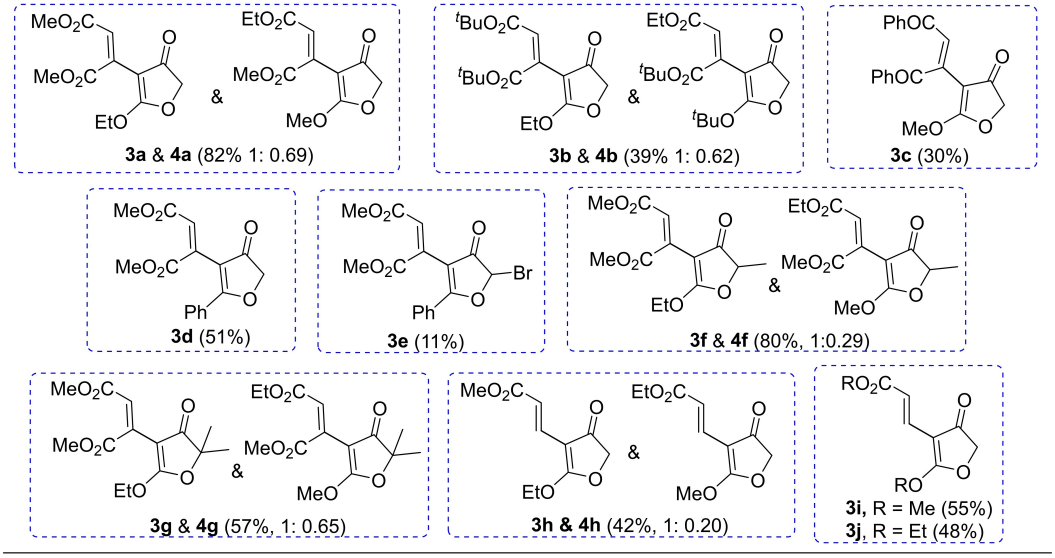
Table 2. Generality of 4-vinyl-3-(2*H*)-furanone synthesis with various activated alkynes.



1a-1e
R1 = OMe, OEt, O^{t}Bu, Ph
R2 = CO_2Me, $CO_2{}^tBu$, COPh, H

2a-2f
X = Cl, Br
R^3 = H, Me
R^4 = H, Me, Br
R^5 = OMe, OEt, Ph

3 **4**

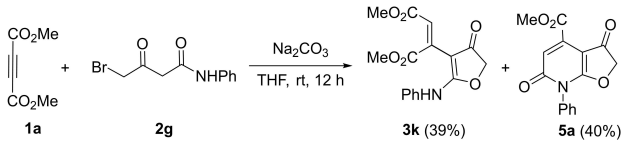


Reaction conditions: **1** (1.0 equiv.), **2** (1.1 equiv.), Na_2CO_3 (2.0 equiv.), THF, rt, 12 h.

ylacetylenedicarboxylate **1a**. These reactions also afforded the furanones **3f** & **4f** and **3g** & **4g** as regioisomeric mixtures of ratio 1:0.29 and 1:0.65 respectively in satisfactory yields. The reaction of methyl propiolate **1d** with ethyl-4-chloroacetoacetate **2a** yielded a 1:0.20 regioisomeric mixture of 4-vinyl-3(2*H*)-furanones **3h** and **4h** in 42% yield. Finally, the reactions of methyl propiolate **1d** with methyl-4-chloroacetoacetate **2f** and ethyl propiolate **1e** with ethyl-4-chloroacetoacetate **2a** afforded corresponding 4-vinyl-3(2*H*)-furanones **3i** and **3j** in 55% and 48% yields respectively.

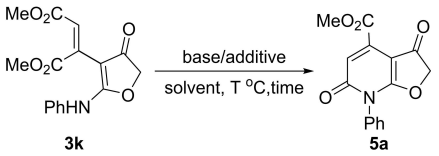
An interesting observation was made when 4-bromo-3-oxo-*N*-phenylbutanamide **2g** was allowed to react with dimethylacetylenedicarboxylate **1a** (Scheme 4). Along with the expected 4-vinyl-3(2*H*)-furanone **3k**, a 3(2*H*)-furanone fused 2-pyridone **5a** was isolated in 40% yield. The structure of **5a** was assigned based on ^{1}H, ^{13}C NMR analyses and mass spectrometry.

On account of the biological importance of the 2-pyridone moiety[14] and intrigued by the formation of this interesting 3(2*H*)-furanone fused pyridone scaffold, we became curious to find suitable conditions to isolate it as the sole product. A detailed study was carried out for the exclusive synthesis of 3(2*H*)-furanone fused 2-pyrridone **5a** from 4-vinyl-3(2*H*)-furanone **3k** by using different bases, solvents, additives and by varying time and temperature (Table 3).



Scheme 4. Synthesis of 4-vinyl-3(2*H*)-furanone and 3(2*H*)-furanone fused 2-pyridone from activated alkyne and 4-bromo-3-oxo-*N*-phenylbutanamide.

Table 3. Conversion of 4-vinyl-3-(2*H*)-furanone **3k** to 2-pyridone fused 3(2*H*)-furanone **5a**.



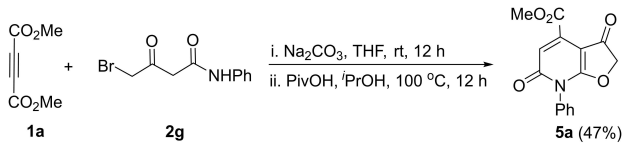
Entry	Base/Additive	Solvent	Yield[a]
1	Na_2CO_3 (1.0 equiv.)	THF	Mixture of **3k** & **5a**
2	Na_2CO_3 (2.0 equiv.)	THF	Mixture of **3k** & **5a**
3	K_2CO_3 (1.0 equiv.)	THF	Mixture of **3k** & **5a**
4	K_3PO_4 (1.0 equiv.)	THF	Mixture of **3k** & **5a**
5	KOH (1.0 equiv.)	THF	NR
6	Cs_2CO_3 (1.0 equiv.)	THF	Mixture of **3k** & **5a**
7	KO^{t}Bu (1.0 equiv.)	THF	NR
8[b]	Na_2CO_3 (2.0 equiv.)	THF	Mixture of **3k** & **5a**
9	*p*TSA (10.0 equiv.)	THF	Mixture of **3k** & **5a**
10[b]	*p*TSA (10.0 equiv.)	THF	Mixture of **3k** & **5a**
11	AcOH (10.0 equiv.)	^{i}PrOH	Mixture of **3k** & **5a**
12[b]	AcOH (10.0 equiv.)	^{i}PrOH	Mixture of **3k** & **5a**
13[c]	AcOH (10.0 equiv.)	^{i}PrOH	**5a (49%)**
14[c]	Pivalic acid (10.0 equiv.)	^{i}PrOH	**5a (70%)**

Reaction conditions: [a] **3k** (0.08 mmol), solvent (2.0 mL), rt, 12 h; [b] 50 °C, 12 h; [c] 100 °C, 12 h.

We first checked the effect of the amount of base used in both reactions with 1.0 and 2.0 equivalents of Na_2CO_3 in THF resulted in incomplete conversions (Table 3, entries 1–2).The screening of bases such as K_2CO_3, K_3PO_4 and Cs_2CO_3 also gave a mixture of **3k** and **5a** whereas with KOH and KO^{t}Bu no reaction was observed (Table 3, entries 3–7). Heating the reaction to 50 °C in the presence of 2.0 equivalents of Na_2CO_3 also furnished an incomplete reaction. Then we added 10.0 equivalents of *p*-TSA as an additive and performed two reactions at rt and 50 °C; both of which failed to afford a complete conversion (Table 3, entries 9–10). In the meantime, we came across an acid mediated 2-pyridone synthesis[15] and hence we tried reactions with 10.0 equivalents of AcOH at rt, 50 °C and 100 °C in ^{i}PrOH (Table 3, entries 11–13). The first two reactions gave a mixture of **3k** and **5a** whereas the reaction at 100 °C afforded the 3(2*H*)-furanone fused 2-pyrridone **5a** in 49% yield. Finally, the reaction with 10.0 equivalents of pivalic acid at 100 °C afforded the expected pyridone fused 3(2*H*)-furanone **5a** in 70% yield (Table 3, entry 14).

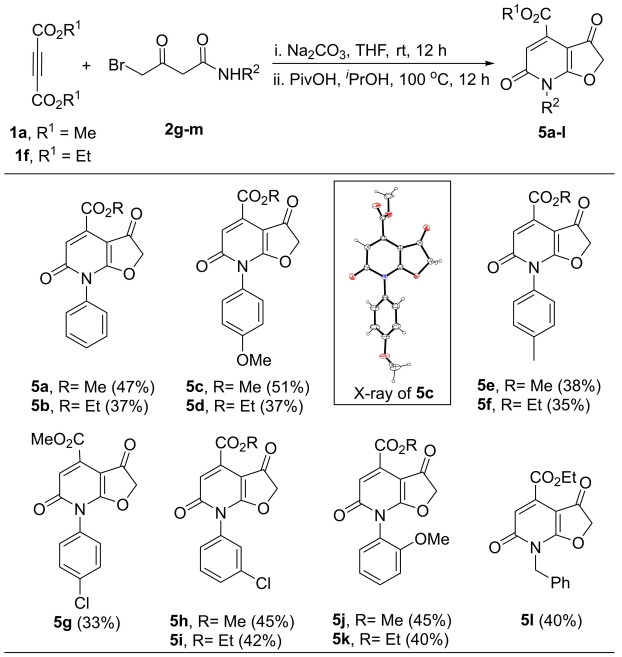
Our next attempt was to develop a one-pot process for synthesizing 3(2*H*)-furanone fused 2-pyrridone from 4-bromo-3-oxo-*N*-phenylbutanamide and an activated alkyne. First, 4-bromo-3-oxo-*N*-phenylbutanamide **2g** was allowed to react with dimethylacetylene dicarboxylate **1a** under the optimized condition for the formation of 4-vinyl-3-(2*H*)-furanone (Scheme 5). After 12 h, the reaction mixture was evaporated and to the crude 10.0 equivalents of pivalic acid followed by ^{i}PrOH as solvent was added and the mixture was allowed to stir at 100 °C for 12 h. From this one-pot reaction, the 3(2*H*)-furanone fused 2-pyrridone **5a** was isolated in 47% yield.

Having developed a sequential one-pot method for the synthesis of 3(2*H*)-furanone fused 2-pyridone analogues, we proceeded by checking the generality with various substituted 4-bromo-3-oxo-*N*-aryl/alkyl-butanamides (Table 4). The reactions of 4-bromo-3-oxo-*N*-phenylbutanamide **2g** with activated alkynes **1a** and **1f** afforded the corresponding 3(2*H*)-furanone fused 2-pyridones **5a** and **5b** in 47% and 37% yields respectively. Different analogues **5c** to **5f** were made in satisfactory yields by introducing electron-donating substituents to the para-position of the aryl ring in 4-bromo-3-oxo-*N*-aryl-butanamide (such as in **2h** and **2i**). We could also provide additional support to the structure with the single crystal X-ray structure of **5c**. Chlorinated analogues of 3(2*H*)-furanone fused 2-pyridones **5g** to **5i** were made by starting from appropriately functionalized 4-bromo-3-oxo-*N*-aryl-butanamides **2j** and **2k**. Methoxy-substituent at the *ortho*-position of 3(2*H*)-furanone fused *N*-aryl-2-pyridone was introduced as in **5j** and **5k** from the reaction of **2l** with **1a** and **1f** respectively. Finally, the



Scheme 5. Synthesis of 3(2*H*)-furanone fused 2-pyridone from activated alkyne and 4-bromo-3-oxo-*N*-phenylbutanamide.

Table 4. Generality of 3(2*H*)-furanone fused 2-pyridone synthesis with various activated alkynes and substituted 4-bromo-3-oxo-*N*-phenylbutanamide.



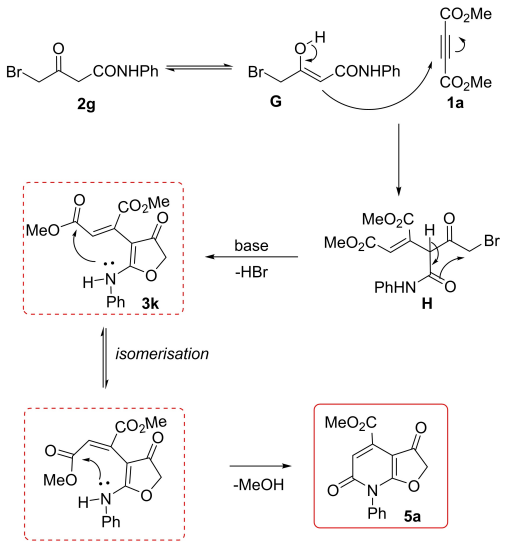
Reaction conditions: i. **1** (1.0 equiv.), **2** (1.1 equiv.), base (2.0 equiv.), THF, rt, 12 h; ii. Pivalic acid (10 equiv.), ^{i}PrOH, 100 °C, 12 h.

reaction of diethylacetylene dicarboxylate **1f** with *N*-benzyl-4-bromo-3-oxobutanamide **2m** provided 3(2*H*)-furanone fused *N*-benzyl-2-pyridone **5l** in 40% yield.

The initial steps towards the formation of 3(2*H*)-furanone fused 2-pyridone are the same as shown in Scheme 3. The Michael adduct **H** is formed by the addition of the enolate **G** to activated alkyne **1a**. Intramolecular nucleophilic substitution occurs in **H** by the attack of ester enolate to the carbon bearing the halogen and this results in the formation of the 3(2*H*)-furanone intermediate **3k**. Acid induced isomerization of the double bond[16] makes the terminal ester-carbonyl closer for the attack of the lone pair on *N*-atom results in the formation of the 3(2*H*)-furanone fused 2-pyridone moiety with simultaneous elimination of MeOH (Scheme 6).

Conclusion

In conclusion, we have developed a method for the synthesis of 4-vinyl-3(2*H*)-furanones from activated alkynes and 4-halo-1,3-dicarbonyl compounds. The expected 4-vinyl-3(2*H*)-furanone forms *via* tandem Michael addition followed by an intramolecular cyclization. We encountered the formation of a side-product (regioisomeric 4-vinyl-3(2*H*)-furanone) by a stepwise [2 + 2] cycloaddition between enolate (of the 4-halo-1,3-dicarbonyl compound) and activated alkyne followed by a sequential 4π-ring opening and an intramolecular cyclization. We also describe the formation of 3(2*H*)-furanone fused 2-pyridone from the reaction of 4-bromo-3-oxo-*N*-alkyl



Scheme 6. Mechanism for the formation of 3-(2*H*)-furanone fused 2-pyridone.

(aryl)butanamide with activated alkynes. The developed methodologies were found to be general affording the differently substituted/fused 3(2*H*)-furanones in satisfactory to good yields; currently the biological evaluation of the synthesized compounds is underway.

Experimental Section

Essential Experimental Procedures/Data. All chemicals were of the best grade commercially available and were used without further purification. All solvents were purified according to the standard procedures; dry solvents were obtained according to the literature methods and stored over molecular sieves. Analytical thin-layer chromatography was performed on polyester sheets precoated with silica gel containing fluorescent indicator (POLYGRAMSIL G/UV254). Gravity column chromatography was performed using silica, and mixtures of ethyl acetate hexanes were used for elution. Melting points were measured with a Fisher John melting point apparatus and are uncorrected. NMR spectra were recorded with Bruker Avance-500 (500 MHz for ^{1}H NMR, 125 MHz for ^{13}C NMR) spectrophotometer instruments. All spectra were measured at 300 K, unless otherwise specified. The chemical shifts δ are given in ppm and referenced to the external standard TMS or internal solvent standard. ^{1}H NMR coupling constants (*J*) are reported in Hertz (Hz) and multiplicities are indicated as follows s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublets). Mass spectra were performed with a Thermo Finnigan MAT95XL, a Thermo Fisher Scientific LTQ Orbitrap Velos, and an Agilent 6890 gas chromatograph with JMS-T100GC spectrometer or with a ESI/HRMS at 60,000 resolution using Thermo Scientific Exactive mass spectrometer with orbitrap analyzer.

All chemicals were purchased from TCI Chemicals, Sigma-Aldrich or Spectrochem. 4-Bromo acetoacetates[17a–b] and 4-bromo-3-oxo-*N*-phenylbutanamide and their derivatives[17c–f] were prepared by following reported procedures.

Experimental procedure for the reaction between activated acetylene and 4-haloacetoacetate: A mixture of activated

acetylene (1.0 equiv.), 4-haloacetoacetate (1.1 equiv.) and sodium carbonate (2.0 equiv.) was weighed into a dry Schlenk tube. The tube was degassed and anhydrous THF (0.18 mM) was added after which the reaction mixture was stirred at RT. Upon completion of the reaction as indicated by TLC (12 h), the solvent was removed and the residue was subjected to column chromatography over silica gel (100–200 mesh), using mixtures of hexanes/ethyl acetate as eluents, affording the corresponding 4-vinyl-3(2*H*)-furanones.

Synthesis and characterization of 4-vinyl-3(2*H*)-furanones

Dimethyl 2-(2-ethoxy-4-oxo-4,5-dihydrofuran-3-yl)maleate & 4-Ethyl 1-methyl 2-(2-methoxy-4-oxo-4,5-dihydrofuran-3-yl)maleate (3 a&4 a): The reaction was performed according to the general procedure with dimethyl acetylenedicarboxylate **1 a** (100 mg, 0.70 mmol), ethyl-4-chloroacetoacetate **2 a** (128 mg, 0.77 mmol) and Na_2CO_3 (150 mg, 1.42 mmol) at room temperature for 12 h. Upon completion of the reaction as indicated by TLC, the solvent was removed and the crude product was purified over silica gel (100–200 mesh) column chromatography (60% ethyl acetate in hexanes) to afford the products **3 a** & **4 a** (157 mg, 82%) as regioisomers in a ratio of 1:0.69. The regioisomers were further purified over 230–400 silica gel column chromatography using 40% ethyl acetate in hexane as eluent, and afforded the two regioisomers **3 a** & **4 a** as colourless solids.

Analytical data of 3 a & 4 a as a mixture:^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 6.88 (s, 1H), 6.83 (s, 0.69H), 4.68 (s, 1.5H), 4.66 (s, 2H), 4.55 (q, J = 6.5 Hz, 2H), 4.20–4.17 (m, 4H), 3.89 (s, 6H), 3.72 (s, 3H), 1.47 (t, J = 7.0 Hz, 3H), 1.28 (t, J = 7.0 Hz, 2.6H); $^{13}C\{^1H\}$NMR ($CDCl_3$, 125 MHz) δ (ppm): 192.0, 191.9, 180.6, 180.3, 167.4, 167.4, 166.6, 166.0, 137.6, 137.0, 113.4, 112.5, 90.5, 90.3, 75.3, 75.2, 68.0, 60.5, 57.8, 52.5, 52.3, 51.6, 14.5, 14.2; HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$calcd for $C_{12}H_{14}O_7Na$: 293.0632; Found: 293.0655. **Dimethyl 2-(2-ethoxy-4-oxo-4,5-dihydrofuran-3-yl)maleate (3 a)**: colourless solid; Mp: 152–154 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 6.88 (s, 1H), 4.66 (s, 2H), 4.55 (q, J = 7.0 Hz, 2H), 3.88 (s, 3H), 3.72 (s, 3H), 1.47 (t, J = 7.0 Hz, 3H); $^{13}C\{^1H\}$NMR ($CDCl_3$, 125 MHz) δ (ppm): 192.0, 180.3, 167.4, 166.6, 137.6, 112.5, 90.0, 75.2, 68.0, 52.4, 51.6, 14.5; HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$calcd for $C_{12}H_{14}O_7Na$: 293.0632; Found: 293.0632.

4-Ethyl 1-methyl 2-(2-methoxy-4-oxo-4,5-dihydrofuran-3-yl)maleate (4 a): Colourless solid; Mp: 124–126 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 6.82 (s, 1H), 4.67 (s, 2H), 4.19–4.15 (m, 5H), 3.88 (s, 3H), 1.27 (t, J = 7.0 Hz, 3H); $^{13}C\{^1H\}$NMR ($CDCl_3$, 125 MHz) δ (ppm): 192.0, 180.7, 167.5, 166.1, 137.0, 113.3, 90.5, 75.3, 60.5, 57.8, 52.5, 14.2; HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$calcd for $C_{12}H_{14}O_7Na$: 293.0632; Found: 293.0643.

The remaining reactions were performed by following the general procedure.

Di-*tert*-butyl 2-(2-ethoxy-4-oxo-4,5-dihydrofuran-3-yl)maleate & 1-(*tert*-butyl) 4-ethyl 2-(2-(*tert*-butoxy)-4-oxo-4,5-dihydrofuran-3-yl)maleate (3 b & 4 b): Regioisomeric mixture (61 mg, 39%, 1:0.62.); ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 6.68 (s, 1H), 6.58 (s, 0.62H), 4.60 (s, 1.2H), 4.56 (s, 2H), 4.49 (q, J = 7.0 Hz, 2H), 4.40 (q, J = 7.0 Hz, 1.2H), 1.49 (s, 9H), 1.42 (s, 5.3H), 1.40–1.37 (m, 18H), 1.34 (t, J = 7.0 Hz, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ (ppm): 192.6, 191.7, 180.3, 180.1, 165.5, 165.2, 164.6, 164.5, 136.4, 132.0, 129.8, 116.1, 91.1, 90.7, 82.1, 81.2, 81.0, 80.0, 75.4, 75.0, 67.7, 66.6, 28.1, 28.0, 27.9, 27.8, 14.8, 14.6; HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$calcd for $C_{18}H_{26}O_7Na$: 377.1571; Found: 377.1574.

(*Z*)-2-(2-methoxy-4-oxo-4,5-dihydrofuran-3-yl)-1,4-diphenylbut-2-ene-1,4-dione (3 c): Pale-yellow viscous liquid (45 mg, 30%); ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): δ 7.94 (2H, d, J = 7.5 Hz), 7.69 (2H, d, J = 8.0 Hz), 7.64 (1H, t, J = 7.0 Hz), 7.53–7.48 (3H, m), 7.41 (2H, t, J = 7.5 Hz), 6.05 (1H, s), 4.88 (2H, s), 3.52 (3H, s); $^{13}C\{^1H\}$NMR ($CDCl_3$, 125 MHz) δ (ppm): 192.5, 185.8, 169.0, 165.3, 153.4, 134.4, 134.2, 132.7, 132.3, 130.2, 129.5, 128.9, 127.6, 101.0, 77.7, 52.4; HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$calcd for $C_{21}H_{16}NaO_5$: 371.0890; Found: 371.0910.

Dimethyl 2-(4-oxo-2-phenyl-4,5-dihydrofuran-3-yl)maleate (3 d): Pale-yellow viscous liquid (109 mg, 51%); ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 7.61–7.58 (m, 2H), 7.46 (t, J = 7.0 Hz, 1H), 7.42–7.37 (m, 2H), 7.03 (s, 1H), 4.74 (s, 2H), 3.65 (s, 3H), 3.48 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ (ppm): δ 198.4,198.0, 182.5, 165.5, 165.1, 133.3, 132.7, 132.4, 131.6, 129.9, 128.8, 128.6, 128.5, 127.7, 124.2, 111.1, 74.6, 52.8, 52.1; HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$calcd for $C_{16}H_{14}O_6Na$: 325.0683; Found: 325.0695.

Dimethyl 2-(5-bromo-4-oxo-2-phenyl-4,5-dihydrofuran-3-yl)maleate (3 e): Pale-yellow viscous liquid (29 mg, 11%); ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): δ 7.70 (d, J = 7.5 Hz, 2H), 7.57 (t, J = 7.5 Hz, 1H), 7.49–7.46 (m, 2H), 7.19 (s, 1H), 6.57 (s, 1H), 3.74 (s, 3H), 3.60 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ (ppm): δ 194.1, 179.2, 164.9, 164.7, 133.2, 132.9, 129.0, 128.7, 128.0, 108.8, 73.1, 53.0, 52.3; HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$calcd for $C_{16}H_{13}BrO_6Na$: 402.9788; Found: 402.9804.

Dimethyl 2-(2-ethoxy-5-methyl-4-oxo-4,5-dihydrofuran-3-yl)maleate & 4-ethyl 1-methyl 2-(2-methoxy-5-methyl-4-oxo-4,5-dihydrofuran-3-yl)maleate (3 f & 4 f): Regioisomeric mixture (161 mg, 80%, 1:0.30); ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): δ 6.87 (s, 1H), 6.78 (s, 0.30H), 4.81–4.73 (m, 1.4H), 4.54 (q, J = 7.0 Hz, 2H), 4.47 (q, J = 7.0 Hz, 0.60 H), 3.89 (s, 3H), 3.80 (s, 1H), 3.74 (s, 1H), 3.72 (s, 3H), 1.57–1.53 (m, 5H), 1.47 (t, J = 7.0 Hz, 3H) 1.40 (t, J = 7.0 Hz, 1H); $^{13}C\{^1H\}$NMR ($CDCl_3$, 125 MHz) δ (ppm): 194.8, 194.4, 179.0, 178.8, 167.5, 166.7, 166.1, 165.4, 138.1, 131.9, 129.0, 128.1, 112.0, 89.0, 84.2, 84.1, 67.8, 66.6, 60.8, 56.6, 52.7, 52.3, 51.8, 51.6, 16.4, 16.2, 14.6, 14.4; HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$calcd for $C_{13}H_{16}O_7Na$: 307.0788; Found: 307.0790.

Dimethyl 2-(2-ethoxy-5,5-dimethyl-4-oxo-4,5-dihydrofuran-3-yl)maleate & 4-Ethyl 1-methyl 2-(2-methoxy-5,5-dimethyl-4-oxo-4,5-dihydrofuran-3-yl)maleate (3 g & 4 g): Regioisomeric mixture (119 mg, 57%, 1:0.65); ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): δ 6.82 (s, 1H), 6.60 (s, 0.65H), 4.22–4.12 (m, 3.4H), 3.77–3.76 (m, 4H), 3.70 (s, 3.4H), 1.94 (s, 3.3H), 1.83 (s, 4H), 1.25 (t, J = 7.0 Hz, 3H), 1.22–1.17 (m, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ (ppm): 198.6, 198.1, 170.4, 169.9, 168.3, 166.5, 166.1, 165.0, 140.3, 140.0, 139.5, 129.6, 129.3, 128.9, 69.4, 65.1, 61.5, 61.1, 61.1, 53.0, 52.9, 52.2, 52.0, 51.0, 33.1, 32.9, 30.7, 30.1, 30.0, 14.1, 14.1; HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$ calcd for $C_{14}H_{18}O_7Na$: 321.0945; Found: 321.0952.

Methyl (*E*)-3-(2-ethoxy-4-oxo-4,5-dihydrofuran-3-yl)acrylate & Ethyl (*E*)-3-(2-methoxy-4-oxo-4,5-dihydrofuran-3-yl)acrylate (3 h & 4 h): Regioisomeric mixture (105 mg, 42%, 1:0.20);^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): δ 7.23–7.17 (m, 1.30H), 6.59–6.54 (m, 1.17H), 4.61 (s, 0.41H), 4.59 (s, 2H), 4.51 (q, J = 7.0 Hz, 2H), 4.15–4.11 (m, 1H), 3.67 (s, 3H), 1.43 (t, J = 7.0 Hz, 3H), 1.22 (t, J = 7.0 Hz, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ (ppm): 192.8, 181.8, 181.6, 168.4, 167.8, 130.6, 130.0, 115.6, 114.8, 92.5, 75.6, 75.5, 67.5, 60.0, 57.2, 51.3, 14.6, 14.3; HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$calcd for $C_{10}H_{12}O_5Na$: 235.0577; Found: 235.0579.

Methyl (*E*)-3-(2-methoxy-4-oxo-4,5-dihydrofuran-3-yl)acrylate (3 i): Colourless solid (129 mg, 55%); Mp: 62–64 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): δ 7.20 (d, J = 16 Hz, 1H), 6.56 (d, J = 15.5 Hz, 1H), 4.62 (s, 2H), 4.12 (s, 3H), 3.67 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ (ppm): 192.8, 181.9, 168.3, 130.3, 115.2, 92.6, 75.6, 57.2, 51.3; HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$calcd for $C_9H_{10}O_5Na$: 221.0420; Found: 221.0425.

Ethyl (*E*)-3-(2-ethoxy-4-oxo-4,5-dihydrofuran-3-yl)acrylate (3 j): pale yellow solid (110 mg, 48%); Mp: 68–70 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): δ 7.21 (d, J = 16 Hz, 1H), 6.57 (d, J = 16 Hz, 1H), 4.59 (s, 2H), 4.51 (q, J = 7.0 Hz, 2H), 4.13 (q, J = 7.0 Hz, 2H), 1.43 (t, J = 7.0 Hz, 3H), 1.22 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ (ppm): 192.8, 181.6, 168.0, 130.2, 115.5, 115.3, 92.5, 75.5, 67.4, 60.0, 14.7, 14.3; HRMS (ESI-Orbitrap) m/z: (M + Na)$^+$calcd for $C_{11}H_{14}O_5Na$: 249.0733; Found: 249.0717.

Dimethyl 2-(4-oxo-2-(phenylamino)-4,5-dihydrofuran-3-yl)maleate (3 k): pale-yellow solid (87 mg, 39%); Mp: 108–110 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): δ 8.83 (brs, 1H), 7.29 (t, J = 7.5 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H), 7.13 (t, J = 7.5 Hz, 1H), 6.79 (s, 1H), 4.56 (s, 2H), 3.83 (s, 3H), 3.64 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ (ppm): 190.8, 173.6, 171.1, 166.8, 136.6, 135.5, 129.4, 125.9, 121.6, 115.9, 89.0, 74.2, 53.5, 51.7; HRMS (ESI-Orbitrap) m/z: (M + Na)$^+$calcd for $C_{16}H_{15}NO_6Na$: 340.0792; Found: 340.0793.

Experimental procedure for the synthesis of 3(2*H*)-furanone fused 2-pyridonefrom activated acetylene and 4-bromo-3-oxo-*N*-phenylbutanamides: A mixture of activated acetylene (1.0 equiv.), 4-bromo-3-oxo-*N*-phenylbutanamide (1.1 equiv.) and sodium carbonate (2.0 equiv.) was weighed into a dry Schlenk tube. The tube was degassed and anhydrous THF (0.18 mM) was added and the reaction mixture was stirred at RT. Upon completion of the reaction (12 h), the solvent was removed and to the residue, isopropanol was added followed by pivalic acid (10 equiv.) and the reaction mixture was allowed to stir at 100 °C for 12 h. Upon completion of the reaction, the solvent was removed and the residue was subjected to column chromatography over silica gel (100–200 mesh), using mixtures of hexanes/ethyl acetate as eluent to afford the corresponding 3(2*H*)-furanone fused 2-pyridone.

Synthesis and characterization of 3(2*H*)-furanone fused 2-pyridones

Methyl 3,6-dioxo-7-phenyl-2,3,6,7-tetrahydrofuro[2,3-*b*]pyridine-4-carboxylate (5 a): The reaction was performed according to the general procedure with dimethyl acetylenedicarboxylate **1 a** (50 mg, 0.35 mmol), 4-bromo-3-oxo-*N*-phenylbutanamide **2 g** (99 mg, 0.39 mmol) and Na_2CO_3 (75 mg, 0.70 mmol) at room temperature for 12 h. Upon completion of the reaction (12 h), the solvent was removed and to the residue isopropanol (2 mL) was added followed by pivalic acid (397 μL, 3.52 mmol) and the reaction mixture was stirred at 100 °C for 12 h. The crude product was purified over silica gel (100–200 mesh) column chromatography (40% ethyl acetate in hexanes) to afford the desired product **5 a** as pale-yellow solid (47 mg, 47%); Mp: 138–142 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): δ 7.51–7.47 (m, 3H), 7.25–7.23 (m, 2H), 6.59 (s, 1H), 4.65 (s, 2H), 3.91 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ (ppm): 187.4, 174.5, 163.9, 161.8, 138.5, 131.8, 130.2, 129.8, 127.6, 115.4, 95.4, 77.0, 53.2; HRMS (ESI-Orbitrap) m/z: (M + Na)$^+$calcd for $C_{15}H_{11}NO_5Na$: 308.0529; Found: 308.0533.

The remaining reactions were performed following this general procedure.

Ethyl 3,6-dioxo-7-phenyl-2,3,6,7-tetrahydrofuro[2,3-*b*]pyridine-4-carboxylate (5 b): Colourless solid (32 mg, 37%); Mp: 128–132 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): δ 7.61–7.55 (m, 3H), 7.33 (d, J = 7.0 Hz, 2H), 6.69 (s, 1H), 4.75 (s, 2H), 4.47 (q, J = 7.0 Hz, 2H), 1.44 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ (ppm): 187.3, 174.5, 163.5, 161.8, 139.0, 131.8, 130.2, 129.8, 127.6, 115.2, 95.5, 77.0, 62.6, 14.0; HRMS (ESI-Orbitrap) m/z: (M + Na)$^+$calcd for $C_{16}H_{13}NO_5Na$: 322.0686; Found: 322.0702.

Methyl 7-(4-methoxyphenyl)-3,6-dioxo-2,3,6,7-tetrahydrofuro[2,3-*b*]pyridine-4-carboxylate(5 c): Pale-yellow solid (56 mg, 51%); Mp: 154–158 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): δ 7.24 (d, J = 8.5 Hz, 2H), 7.08 (d, J = 8.5 Hz, 2H), 6.69 (s, 1H), 4.75 (s, 2H), 4.01 (s, 3H), 3.89 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ (ppm): 187.4, 174.8, 164.0, 162.1, 160.6, 138.4, 128.7, 124.0, 115.4, 115.1, 95.4, 77.0, 55.6, 53.2; HRMS (ESI-Orbitrap) m/z: (M + Na)$^+$calcd for $C_{16}H_{13}NO_6Na$: 338.0635; Found: 338.0642.

Ethyl 7-(4-methoxyphenyl)-3,6-dioxo-2,3,6,7-tetrahydrofuro[2,3-*b*]pyridine-4-carboxylate (5 d): Pale-yellow solid (32 mg, 37%); Mp: 116–118 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): δ 7.24 (d, J = 8.0 Hz, 2H), 7.08 (d, J = 8.0 Hz, 2H), 6.68 (s, 1H), 4.74 (s, 2H), 4.47 (q, J = 7.0 Hz, 2H), 3.89 (s, 3H), 1.43 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ (ppm): 187.4, 174.7, 163.5, 162.1, 160.6, 138.9, 128.7, 124.0, 115.0, 95.5, 77.0, 62.5, 55.6, 14.0; HRMS (ESI-Orbitrap) m/z: (M + H)$^+$calcd for $C_{17}H_{16}NO_6$: 330.0972; Found: 330.0968.

Methyl 3,6-dioxo-7-(*p*–tolyl)-2,3,6,7-tetrahydrofuro[2,3-*b*]pyridine-4-carboxylate (5 e): Pale-yellow solid (40 mg, 38%); Mp: 160–164 °C;^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): δ 7.39 (d, J = 8.0 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 6.68 (s, 1H), 4.74 (s, 2H), 4.00 (s, 3H), 2.46 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ (ppm): 187.3, 174.6, 164.0, 161.9, 140.5, 138.4, 130.5, 129.0, 127.3, 115.5, 95.4, 53.2, 21.3; HRMS (ESI-Orbitrap) m/z: (M + Na)$^+$calcd for $C_{16}H_{13}NO_5Na$: 322.0686; Found: 322.0693.

Ethyl 3,6-dioxo-7-(*p*–tolyl)-2,3,6,7-tetrahydrofuro[2,3-*b*]pyridine-4-carboxylate (5 f): Colourless solid (31 mg, 35%); Mp: 160–164 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): δ 7.30 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 8.0 Hz, 2H), 6.59 (s, 1H), 4.65 (s, 2H), 4.38 (q, J = 7.0 Hz, 2H), 2.37 (s, 3H), 1.34 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ (ppm): 187.3, 174.6, 163.5, 162.0, 140.5, 138.9, 130.5, 129.1, 127.3, 115.2, 95.5, 77.0, 62.5, 21.3, 14.0; HRMS (ESI-Orbitrap) m/z: (M + Na)$^+$calcd for $C_{17}H_{15}NO_5Na$: 336.0842; Found: 336.0849.

Methyl 7-(4-chlorophenyl)-3,6-dioxo-2,3,6,7-tetrahydrofuro[2,3-*b*]pyridine-4-carboxylate (5 g): Colourless solid (37 mg, 33%); Mp: 168–172 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): δ 7.56 (d, J = 8.5 Hz, 2H), 7.29–7.27 (m, 2H), 6.69 (s, 1H), 4.76 (s, 2H), 4.00 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ (ppm): 187.2, 174.3, 163.8, 161.5, 138.7, 136.4, 130.1, 130.0, 129.1, 115.4, 95.5, 77.0, 53.2; HRMS (ESI-Orbitrap) m/z: (M + H)$^+$calcd for $C_{15}H_{11}ClNO_5$: 320.0320; Found: 320.0320.

Methyl 7-(3-chlorophenyl)-3,6-dioxo-2,3,6,7-tetrahydrofuro[2,3-*b*]pyridine-4-carboxylate (5 h): Pale yellow solid (50 mg, 45%); Mp: 148–152 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): δ 7.56–7.51 (m, 2H), 7.36 (s, 1H), 7.25 (d, J = 7.0 Hz, 2H) 6.69 (s, 1H), 4.77 (s, 2H), 4.01 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ (ppm): 187.1, 174.2, 163.8, 161.4, 138.7, 135.4, 132.6, 130.7, 130.5, 128.1, 126.1, 115.4, 95.5, 77.1, 53.3; HRMS (ESI-Orbitrap) m/z: (M + Na)$^+$calcd for $C_{15}H_{10}ClNO_5Na$: 342.0140; Found: 342.0240.

Ethyl 7-(3-chlorophenyl)-3,6-dioxo-2,3,6,7-tetrahydrofuro[2,3-*b*]pyridine-4-carboxylate (5 i): Pale-yellow solid (40 mg, 42%); Mp: 116–118 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): δ 7.47–7.42 (m, 2H), 7.27 (s, 1H), 7.15 (d, J = 7.0 Hz, 2H), 6.59 (s, 1H), 4.68 (s, 2H), 4.38 (q, J = 7.0 Hz, 2H), 1.34 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ (ppm): 187.1, 174.2, 163.3, 161.5, 139.2, 135.4, 132.7, 130.7, 130.5, 128.1, 126.1, 115.2, 95.6, 77.1, 62.6, 14.0; HRMS (ESI-Orbitrap) m/z: (M + H)$^+$calcd for $C_{16}H_{13}ClNO_5$: 334.0477; Found: 334.0476

Methyl 7-(2-methoxyphenyl)-3,6-dioxo-2,3,6,7-tetrahydrofuro[2,3-*b*]pyridine-4-carboxylate (5 j): Pale-yellow solid (50 mg, 45%); Mp: 182–186 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): δ 7.44 (t, J = 7.0 Hz, 1H), 7.17 (d, J = 7.5 Hz, 1H), 7.05–7.01 (m, 2H) 6.58 (s, 1H), 4.63 (s, 2H), 3.91 (s, 3H), 3.74 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ (ppm): 187.5, 175.0, 164.1, 161.5, 154.4, 138.4, 131.8, 129.1, 121.1, 120.4, 115.4, 112.3, 95.3, 56.0, 53.2; HRMS (ESI-Orbitrap) m/z: (M + Na)$^+$calcd for $C_{16}H_{14}NO_6$: 316.0816; Found: 316.0812.

Ethyl 7-(2-methoxyphenyl)-3,6-dioxo-2,3,6,7-tetrahydrofuro[2,3-*b*]pyridine-4-carboxylate (5k): Pale-yellow solid (37 mg, 40%); Mp: 130–132 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): δ 7.44 (t, J = 7.5 Hz, 1H), 7.17 (d, J = 8.0 Hz, 1H), 7.06–7.02 (m, 2H), 6.58 (s, 1H), 4.63 (s, 2H), 4.38 (q, J = 7.0 Hz, 2H), 3.75 (s, 3H), 1.35 (t, J = 7.0 Hz,3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ (ppm): 187.4, 175.0, 163.7, 161.6, 154.5, 138.9, 131.8, 129.1, 121.1, 120.5, 115.2, 112.4, 95.3, 77.0, 62.4, 55.9, 14.0; HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$calcd for $C_{17}H_{15}NO_6Na$: 352.0792; Found: 352.0795.

Ethyl 7-benzyl-3,6-dioxo-2,3,6,7-tetrahydrofuro[2,3-*b*]pyridine-4-carboxylate) (5l): Pale-yellow liquid (35 mg, 40%); ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): δ 7.43 (d, J = 6.5 Hz, 2H), 7.38–7.35 (m, 3H), 6.62 (s, 1H) 5.26 (s, 2H), 4.83 (s, 2H), 4.43 (q, J = 7.0 Hz, 2H), 1.40 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ (ppm): 187.2, 174.5, 163.5, 161.8, 138.5, 134.4, 128.9, 128.7, 128.5, 114.8, 95.6, 62.5, 44.7, 14.0; HRMS (ESI-Orbitrap) m/z: $(M+H)^+$calcd for $C_{17}H_{16}NO_5$: 314.1023; Found: 314.1023.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: 3(2*H*)-Furanones · 4-Halo-1, 3-dicarbonyl compounds · 2-Pyridone · activated acetylene · tandem reaction

[1] For earlier summaries of the literature, see: a) D. W. Henry, R. M. Silverstein, *J. Org. Chem.* **1966**, *31*, 2391; b) Y. Li, K. J. Hale, *Org. Lett.* **2007**, *9*, 1267; c) D. C. Sass, V. C. G. Heleno, J. L. C. Lopes, M. G. Constantino, *Tetrahedron Lett.* **2008**, *49*, 3877; d) A. Husain, S. A. Khan, F. Iram, A. Iqbal, M. Asif, *Eur. J. Med. Chem.* **2019**, *171*, 66.
[2] T. Brandt, W. I. Taylor, *J. Chem. Soc.* **1954**, 3425.
[3] V. K. Omanakuttan, J. John, H. Hopf, *Eur. J. Org. Chem.* **2021**, 163.
[4] a) R. F. W. Jackson, R. A. Raphael, *Tetrahedron Lett.* **1983**, *24*, 2117; b) R. A. Mack, W. I. Zazulak, L. A. Radov, J. E. Baer, J. D. Stewart, P. H. Elzer, C. R. Kinsolving, V. S. Georgiev, *J. Med. Chem.* **1988**, *31*, 1910; c) S. W. Felman, I. Jirkovsky, K. A. Memoli, L. Borella, C. Wells, J. Russell, J. Ward, *J. Med. Chem.* **1992**, *35*, 1183; d) D. Villemin, P.-A. Jaffrès, M. Hachémi, *Tetrahedron Lett.* **1997**, *38*, 537; e) H. T. Sakamoto, D. Flausino, E. E. Castellano, C. B. W. Stark, P. J. Gates, N. P. Lopes, *J. Nat. Prod.* **2003**, *66*, 693; f) S. S. Shin, Y. Byun, K. M. Lim, J. K. Choi, K.-W. Lee, J. H. Moh, J. K. Kim, Y. S. Jeong, J. Y. Kim, Y. H. Choi, H.-J. Koh, Y. .-H. Park, Y. I. Oh, M.-S. Noh, S. Chung, *J. Med. Chem.* **2004**, *47*, 792.
[5] T. T. Haug, S. F. Kirsch, *Targets in Heterocyclic Systems*, Vol. 13, (Eds: O. A. Attanasi, D. Spinelli), Società Chimica Italiana, Roma, Italy **2009**, p. 57–91.
[6] For selected reports on the total synthesis of 3(2*H*)-furanone containing natural products see: a) H. Saimoto, T. Hiyama, H. Nozaki, *J. Am. Chem. Soc.* **1981**, *103*, 4975; b) P. J. Jerris, A. B. Smith III, *J. Org. Chem.* **1981**, *46*, 577; c) R. F. W. Jackson, R. A. Raphael, *J. Chem. Soc. Perkin Trans. 1* **1984**, *1*, 535; d) A. F. Thomas, H. Damm, *Tetrahedron Lett.* **1986**, *27*, 505; e) Y. Inoue, K. Ohuchi, I.-F. Yen, S. Imaizumi, *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3518; f) S. Manfredini, P. G. Baraldi, R. Bazzanini, M. Guarnen, D. Simoni, J. Balzarini, E. D. Clercq, *J. Med. Chem.* **1994**, *37*, 2401; g) K. Hirai, H. Ooi, T. Esumi, Y. Iwabuchi, S. Hatakeyama, *Org. Lett.* **2003**, *5*, 857.
[7] For selected reports on the synthesis of 3(2*H*)-furanones see: a) R. Antonioletti, F. Bonadies, T. Prencipe, A. Scettri, *J. Chem. Soc. Chem. Commun.* **1988**, 850; b) J. D. Winkler, K. Oh, S. M. Asselin, *Org. Lett.* **2005**, *7*, 387; c) M. Poonoth, N. Krause, *J. Org. Chem.* **2011**, *76*, 1934; d) Y. Liu, M. Liu, S. Guo, H. Tu, Y. Zhou, H. Gao, *Org. Lett.* **2006**, *8*, 3445; e) S. F. Kirsch, J. T. Binder, C. Liébert, H. Menz, *Angew. Chem. Int. Ed.* **2006**, *45*, 5878; f) F. Silva, M. Reiter, R. Mills-Webb, M. Sawicki, D. Klär, N. Bensel, A. Wagner, V. Gouverneur, *J. Org. Chem.* **2006**, *71*, 8390; g) C. M. Marson, E. Edaan, J. M. Morrell, S. J. Coles, M. B. Hursthouse, D. T. Davies, *Chem. Commun.* **2007**, 2494; h) A. Picado, S. J. Li, R. K. Dieter, *J. Org. Chem.* **2016**, *81*, 1391; i) Q. .-Q. Zhou, M. Cheng, Q. Liu, B. .-Q. Qu, X. .-Y. Huang, F. Yang, K. Ji, Z. .-S. Chen, *Org. Lett.* **2021**, *23*, 9151.
[8] X. Dou, X. Han, Y. Lu, *Chem. Eur. J.* **2012**, *18*, 85.
[9] Y. Yan, R. Lu, J. Wang, Y. Xuan, M. Yan, *Tetrahedron* **2012**, *68*, 6123.
[10] J. John, H. Hopf, *Eur. J. Org. Chem.* **2013**, 2013, 841.
[11] J. John, E. Târcoveanu, P. G. Jones, H. Hopf, *Beilstein J. Org. Chem.* **2014**, *10*, 1462.
[12] J. John, V. K. Omanakuttan, T. Aneeja, C. H. Suresh, P. G. Jones, H. Hopf, *J. Org. Chem.* **2019**, *84*, 5957.
[13] a) K. C. Brannock, R. D. Burpitt, V. W. Goodlett, J. G. Thweatt, *J. Org. Chem.* **1963**, *28*, 1464; b) K. C. Brannock, R. D. Burpitt, V. W. Goodlett, J. G. Thweatt, *J. Org. Chem.* **1963**, *28*, 1464; c) R. D. Clark, K. G. Untch, *J. Org. Chem.* **1979**, *44*, 253; d) M. Miesch, F. Wendling, M. Franck-Neumann, *Tetrahedron Lett.* **1999**, *40*, 839.
[14] a) H. G. Jessen, K. Gademann, *Nat. Prod. Rep.* **2010**, *27*, 1168; b) Q. Li, L. A. Mitscher, L. L. Shen, *Med. Res. Rev.* **2000**, *20*, 231; c) J. L. Medina-Franco, K. Martínez-Mayorga, C. Juárez-Gordiano, R. Castillo, *ChemMedChem* **2007**, *2*, 1141; d) L. Ackermann, A. V. Lygin, N. Hofmann, *Org. Lett.* **2011**, *13*, 3278; e) Z. Zhang, S. Fang, Q. Liu, G. Zhang, *J. Org. Chem.* **2012**, *77*, 7665; f) Q. Chong, X. Xin, C. Wang, F. Wu, B. Wan, *RSC Adv.* **2013**, *3*, 21222; g) M. Fujii, T. Nishimura, T. Koshiba, S. Yokoshima, T. Fukuyama, *Org. Lett.* **2013**, *15*, 232; h) S. Zhou, D. Y. Liu, S. Wang, J. S. Tian, T. P. Loh, *Chem. Commun.* **2020**, *56*, 15020; i) Y. Shang, Y. C. Wu, Q. Gao, C. Liu, L. Li, X. Zhang, H. G. Cheng, S. Liu, Q. Zhou, *Nat. Commun.* **2021**, *12*, 2988.
[15] R. Manikandan, M. Jeganmohan, *Org. Lett.* **2014**, *16*, 3568.
[16] a) Z.-T. Huang, Z.-R. Liu, *Heterocycles* **1986**, *24*, 2247; b) T. Tokumitsu, S. Nagao, *Bull. Chem. Soc. Jpn.* **1993**, *66*, 2118.
[17] a) R. A. Mack, W. I. Zazulak, L. A. Radov, J. E. Baer, J. D. Stewart, P. H. Elzer, *J. Med. Chem.* **1988**, *31*, 1918; b) H. Y. Choi, D. Y. Chi, *Org. Lett.* **2003**, *5*, 411; c) V. Madhura, H. M. Revankar, M. V. Kulkarni, *Z. Naturforsch. B.* **2015**, *70*, 483; d) A. S. Patel, N. P. Kapuriya, Y. T. Naliapara, *J. Heterocycl. Chem.* **2017**, *54*, 2635; e) M. I. Ali, M. A. Abou-state, N. M. Hassan, *J. Chem. Eng. Data.* **1972**, *17*, 106; f) D. Brough, S. M. Allan, S. Freeman, A. G. Baldwin, U. S. Patent No: US 2018/0215772 Al, Aug. 2, **2018**; g) B. Alexander, W. J. B. Reis, L. D. Alexander, M. Jonathan, S. Jean-Marie, M. William, WIPO, International Publication Number: WO 2013/002660 A2, Jan. 3, **2013**.

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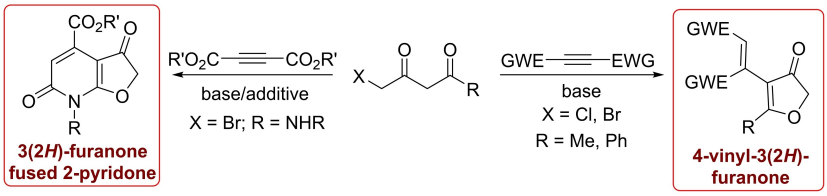
RESEARCH ARTICLE



Synthesis of 4-vinyl-3(2*H*)-furanones from 4-halo-1,3-dicarbonyl compounds with alkynes was achieved *via* a tandem Michael addition and intramolecular cyclization pathway. In addition, a regioisomer formation of the same product *via* a stepwise [2 + 2] cycloaddition, sequential 4π-ring opening, and an intramolecular cyclization has also been noted. Formation of 3(2*H*)-furanone fused 2-pyridone from the reaction of 4-bromo-3-oxo-*N*-alkyl (aryl) butanamide with activated alkynes was also realised.

V. K. Omanakuttan, Dr. P. V. Santhini, S. Shaludheen, Dr. S. Varughese, Prof. Dr. H. Hopf*, Dr. J. John**

1 – 9

Tandem Reaction of 4-Halo-1,3-Dicarbonyl Compounds with Alkynes towards 4-Vinyl-3(2*H*)-Furanones and 3(2*H*)-Furanone fused 2-Pyridones

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3(2*H*)-Furanone Synthesis

Synthesis of 3(2*H*)-Furanones: A Review

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Dedicated to the memory of Professor Rolf Huisgen

Abstract: The present review describes the methods reported for the synthesis of 3(2*H*)-furanones. This heterocycle forms the core structure of a number of natural products and biologically active scaffolds. We have covered all reports available on the synthesis of 3(2*H*)-furanone derivatives and have divided the review into several sections based on the substitution patterns present in the heterocycle. Special emphasis is given to the generality and the mechanistic rationalizations of each methodology. In addition, all total syntheses reported for the synthesis of 3(2*H*)-furanone containing natural products are reviewed by highlighting the heterocycle synthesis.

1. Introduction

Furanones are an important class of oxygen containing heterocycles, which form the core structure of many naturally occurring motifs starting from the simple 2,5-dimethyl-4-hydroxy-3(2*H*)-furanone (DMHF, a flavor and aroma agent), to ascorbic acid and complex natural products such as eremantholide A.[1] Furanone moieties constitute the pharmacophores of many biologically active molecules covering various therapeutic categories such as analgesic, anti-inflammatory, anticancer, anticonvulsant, antibacterial, antifungal, antioxidant, antiulcer, and antituberculosis compounds.[2] As a result, these heterocycles have received considerable attention by organic chemists in the past as intriguing synthetic targets. Chemically, they are derivatives of furan and, depending on the structure, they can be classified into three main types: (i) 2(3*H*)-furanones **1**, (ii) 2(5*H*)-furanones **2**, and (iii) 3(2*H*)-furanones **3** (Figure 1).[3] Due to our continued interest in the chemistry of 3(2*H*)-furanones, we have reviewed the synthetic methodologies for accessing this particular heterocycle in detail.

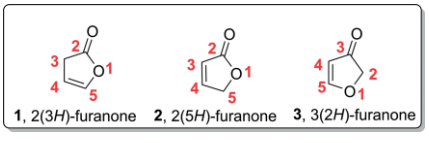

Figure 1. Three types of furanones.

The 3(2*H*)-furanone unit is found in a plethora of natural products, biologically active scaffolds, and fluorophores. A selection of important natural products containing the 3(2*H*)-furanone core unit is collected in Figure 2: bullatenone **4**, inotilone **5**, geiparvarin **6**, hyperolactone C **7**, nemoralisin A **8**, trachyspic acid **9**, pseurotin A **10**, griseofulvin **11**, eremantholide A **12**, ciliarin **13**, jatrophone **14** and parvifloranine A **15**; some of these compounds are considered as promising pharmaceutical candidates (Figure 2). The potent biological activities (eg. Anti-tumor) of 3(2*H*)-furanones have been linked with their ability to act as Michael acceptors.[4] It has also been found that various substituents at specified positions on the furanone moiety cause marked improvements in the pharmacological effects of these heterocyclic systems. All these properties have made 3(2*H*)-furanones a challenging target for synthetic chemists for more than 5 decades and the first review on the topic came in 2009 from Haug and Kirsch.[5] Over these years, a number of synthetic methodologies involving acid or base mediated, Lewis acid or base catalyzed, metal-free or metal-catalyzed processes were developed for accessing functionalized 3(2*H*)-furanones. In addition, a number of well-designed tandem approaches, one-pot routes and enantioselective syntheses were also established. By utilizing all these developed synthetic strategies, the total syntheses of most of the 3(2*H*)-furanone containing natural products have been accomplished.

The intention of this review is to outline all methodologies reported for the synthesis of the 3(2*H*)-furanone moiety. The review is organized into sections based on the substitution patterns present in the 3(2*H*)-furanone core. Accordingly, we have prepared several sections describing the synthesis of (i) unsubstituted-3(2*H*)-furanones; (ii) 2-substituted-3(2*H*)-furanones; (iii) 4-substituted-3(2*H*)-furanones; (iv) 5-substituted-3(2*H*)-furanones; (v) 2,4-disubstituted-3(2*H*)-furanones; (vi) 2,5-disubstituted-3(2*H*)-furanones; (vii) 4,5-disubstituted-3(2*H*)-furanones;

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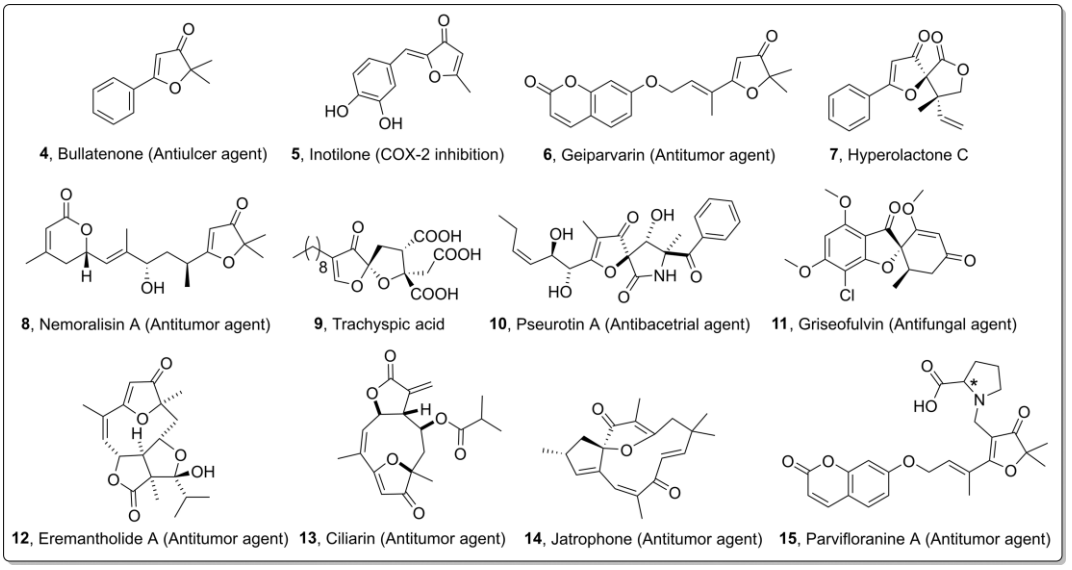

Figure 2. Natural products containing a 3(2*H*)-furanone core.

(viii) 2,4,5-trisubstituted-3(2*H*)-furanones. We have also covered all total syntheses of natural products containing a 3(2*H*)-furanone core unit with special emphasis on the methodology of the synthesis of the heterocycle.

2. Methods for the Synthesis of Unsubstituted-3(2*H*)-furanones

In 1981, Meister and Scharf reported the synthesis of unsubstituted 3(2*H*)-furanone **3** from 5-methoxy-3-oxo-tetrahydrofuran **16** (Scheme 1).[6] The reaction was effected by a base-catalyzed elimination of MeOH by pyrolysis in the presence of a sodium-ammonium-hydrogenphosphate ($NaNH_4HPO_4$) buffer. Because of the known ease of polymerization of the enolizable 3(2*H*)-furanone special reaction conditions were required for its preparation from **16**. The accompanying polymerization was partially held at bay by the addition of glycerol. By starting with appropriately substituted 5-methoxy-3-oxo-tetrahydrofurans the authors could synthesize 2-substituted, 4-substituted, 2,2-disubstituted, and 5-substituted-3(2*H*)-furanones.

An easy access of unsubstituted 3(2*H*)-furanone was also reported by Taddei and co-workers in 1986 (Scheme 2).[7] The target molecule **3** was synthesized in their approach by the protonolysis of 3-trimethylsiloxy-furan **18**. The treatment of

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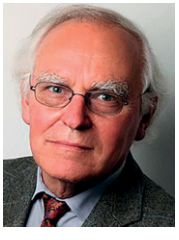
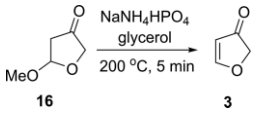
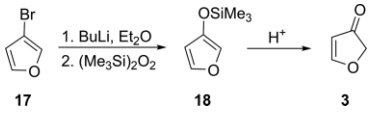


Henning Hopf is a retired university professor at the Technical University of Braunschweig in Germany. He studied at Göttingen University and received his Ph. D. degree at the University of Wisconsin in Madison, U.S.A. After his return to Germany he worked at the Universities of Marburg and Karlsruhe before becoming a professor of organic chemistry at Würzburg. From 1979 to his retirement (2005) he was the Director of the Institute of Organic Chemistry at Braunschweig. He has been the President of the German Chemical Society (2004), and received numerous national and international prizes and awards. His main area of research has been the study of unsaturated hydrocarbons (alkynes, allenes, cumulenes, radialenes, dendralenes, polyolefins, retinoids, bridged aromatic compounds, and thermal rearrangements).



Scheme 1. Synthesis of 3(2*H*)-furanone **3** from 5-methoxy-3-oxo-tetrahydrofuran **16**.

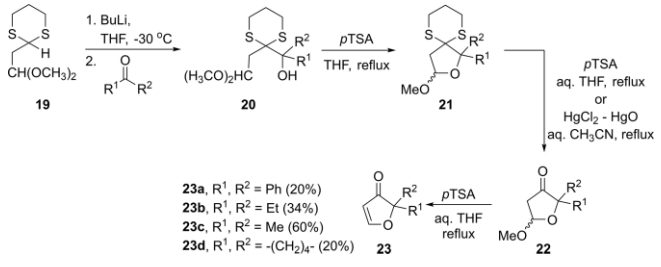
3-bromofuran **17** with BuLi generated the corresponding heterocyclic anion which was trapped by bis(trimethylsilyl) peroxide to furnish the 3-trimethylsiloxy-furan **18**.



Scheme 2. Synthesis of 3(2*H*)-furanone from 3-trimethylsiloxy-furan **18**.

3. Methods for the Synthesis of 2-Substituted-3(2*H*)-furanones

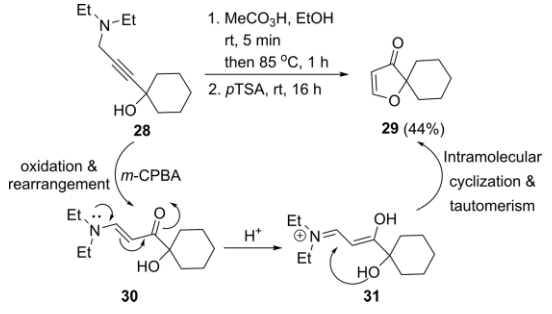
An approach towards 2,2-disubstituted-3(2*H*)-furanones starting from 2,2-dimethoxymethyl-1,3-dithiane was published in 1973 by Sher et al. (Scheme 3).[8] This route began with the generation of a carbanion by treatment of 2,2-dimethoxymethyl-1,3-dithiane **19** with BuLi after which the former was treated in situ with a ketone to furnish the corresponding secondary alcohol **20**. Cyclic acetal **21** was then synthesized by treating **20** with *p*TSA in refluxing THF. Subsequently, the thioacetal moiety was cleaved by either *p*TSA treatment or with mercuric salts. Finally, 2,2-disubstituted-3(2*H*)-furanones **23** were synthesized from 3-oxo-furan **22** by the reaction with *p*TSA in refluxing aqueous THF. The overall yield was found to be better with a Me-substituent than with phenyl.



Scheme 3. Synthesis of 2,2-disubstituted-3(2*H*)-furanones **23** from 2,2-dimethoxymethyl-1,3-dithiane **19**.

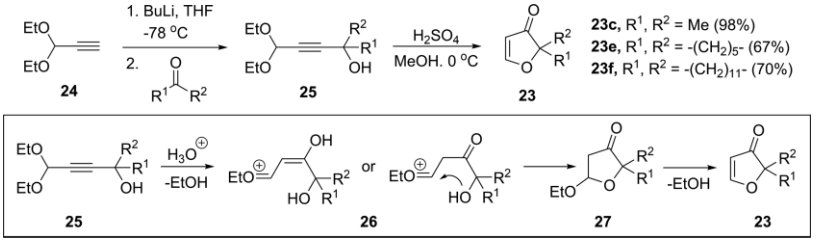
Hiyama and co-workers reported another route for the synthesis of 2,2-disubstituted-3(2*H*)-furanones from propargylic alcohols **25** (Scheme 4).[9] The addition of the lithiated propynal diethyl acetal **24** to different ketones furnished the corresponding 4-hydroxy-2-alkynyl diethyl acetals **25**. 2,2-disubstituted-3(2*H*)-furanones **23** were subsequently obtained by an acid (H_2SO_4) induced intramolecular cyclization of the propargylic alcohol. The steric bulk of the dialkyl substituents on the propargylic alcohol seemed to decrease the yield of the intramolecular cyclization. The course of the reaction starts with the hydration of the acetylenic moiety and elimination of one ethanol equivalent to furnish the intermediate **26**. This is followed by intramolecular cyclization in **26** by the nucleophilic attack of the hydroxyl group to form the 5-ethoxydihydrofuranone **27** from which ethanol is finally eliminated to yield the 2,2-disubstituted-3(2*H*)-furanone **23**.

Inspired by the synthesis of 2,2-disubstituted-3(2*H*)-furanones from propargylic alcohols, Chen et al. reported an interesting improvement (Scheme 5).[10] They found that propargylamines could be converted to enaminones easily by oxidation with *m*-CPBA or peracetic acid. By combining this transformation and the above mentioned intramolecular cyclization in one-pot, they demonstrated that α-hydroxylated propargylamine **28** could be converted to 2-spirocyclic-3(2*H*)-furanone **29**. The first stage involves the conversion of **28** to the intermediate enaminone **30** which is subsequently treated with *p*TSA to afford the final 2-spirocyclic-3(2*H*)-furanone **29**.



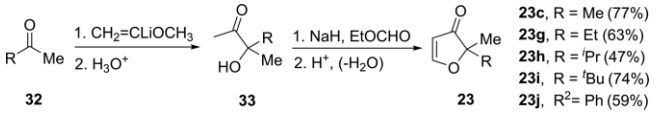
Scheme 5. Synthesis of spirocyclic-3(2*H*)-furanone **29** from an α-hydroxylated propargylamine.

A three step synthetic route towards racemic 2,2-disubstituted-3(2*H*)-furanones has been reported by Baldwin and Mazzuckelli in 1986 (Scheme 6).[11] Their sequence started with the addition of 1-methoxyvinyllithium to different substituted ketones **32** to afford the corresponding α-hydroxy methyl ketones **33**. 2,2-disubstituted-3(2*H*)-furanones were next synthe-



Scheme 4. Synthesis of 2,2-disubstituted-3(2*H*)-furanones **23** from propargylic alcohols **25**.

sized by subjecting the α-hydroxy methylketones **33** to formylation and successive dehydration in one-pot. The yields of 2,2-disubstituted-3(2*H*)-furanones were found to decrease with an increase in the steric bulk of the R-group, but, unexpectedly, the ^{t}Bu-group-substituted intermediate gave yields similar to those observed for methyl-substituted compounds. The synthesized 2,2-disubstituted-3(2*H*)-furanones were then subjected to [2+2] photoannelation with alkenes.



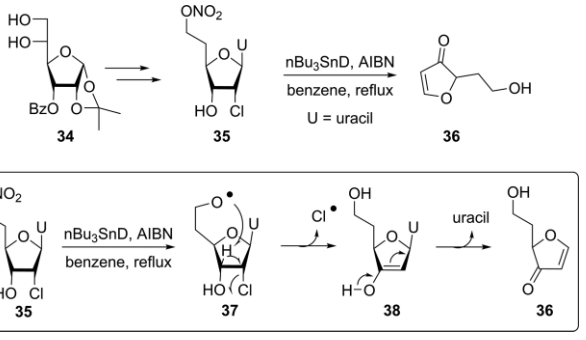
Scheme 6. Synthesis of 2,2-disubstiuted-3(2*H*)-furanones **23** from α-hydroxy methylketones **33**.

During the investigations to unravel the inactivation of ribonucleotide reductases by 2′-chloro-2′-deoxynucleotides, Robins and co-workers observed the formation of 2-substituted-3(2*H*)-furanone via a radical pathway (Scheme 7).[12] α-D-Allofuranose derivative **34** was converted into 1-(2-chloro-2-deoxy-6-O-nitro-β-D-ribohexofuranosyl)uracil **35** by a series of synthetic transformations. 2-(2-hyrdoxyethyl)-3(2*H*)-furanone **36** was prepared from **35** by the reaction with *n*Bu_3SnD and AIBN in refluxing benzene. The mechanism of the conversion of **35** to 2-substituted-3(2*H*)-furanone **36** starts with the generation of the 6′-alkoxy radical **37** upon treating **35** with *n*Bu_3SnD and AIBN. This radical next abstracts the H3′ hydrogen atom by a 1,5 hydrogen atom transfer process. The enol **38** is then formed by elimination of a chlorine radical, and finally tautomerisation of the enol furnishes the 2-substituted-3(2*H*)-furanone **36** by the expulsion of uracil moiety.

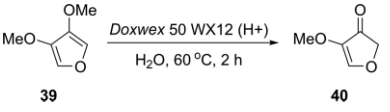
4. Methods for the Synthesis of 4-Substituted-3(2*H*)-furanones

The synthesis of 4-methoxy-3(2*H*)-furanone from 3,4-dimethoxy furan was reported in 1978 by Eugster et al. The hydrolysis of one methoxy-group in 3,4-dimethoxy furan **39** by treatment with Dowex resin (acidic) in water at 60 °C furnished 4-methoxy-3(2*H*)-furanone **40** after 2 h (Scheme 8).[13]

Simoni and co-workers later reported different strategies for the preparation of 4-substituted derivatives from ethyl 2,4-dioxoalkanoates (Scheme 9).[14] The reaction was initiated by the protection of β-diketones to 3,5-disubstituted isoxazoles **42** using hydroxylamine hydrochloride. Then the ester functionality



Scheme 7. Synthesis of 2-substituted-3(2*H*)-furanone **36** by a radical pathway.

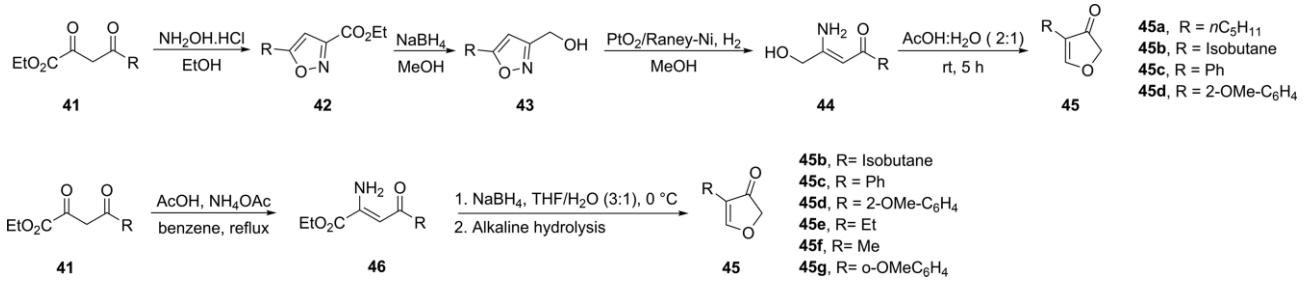


Scheme 8. Synthesis of 4-methoxy-3(2*H*)-furanone **40** from 3,4-dimethoxy-furan **39**.

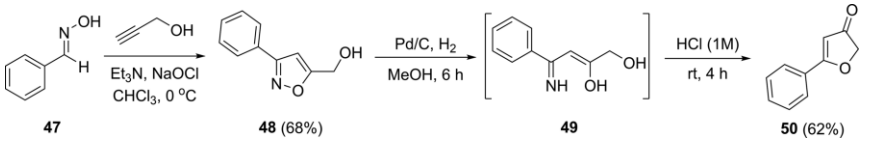
in **42** was converted into the corresponding primary alcohol **43** by reduction with sodium borohydride. This was followed by the hydrogenation of primary alcohol **43** with a PtO_2/Raney-Ni catalyst into β-enamino-ketone **44**. Finally, acid catalysed cyclodehydration of β-enamino-ketone **44** provided the corresponding 4-substituted-3(2*H*)-furanones **45**. The authors also showed that **45** could be accessed by another pathway without an isoxazole intermediate. Towards this end, 1,3-diketones were converted into the corresponding enaminones **46**. Later, upon treating **46** with sodium borohydride at 0 °C, followed by aqueous alkaline treatment resulted in the corresponding 4-substituted-3(2*H*)-furanones **45**. In the same report, it was also shown that 2,4-disubstituted-3(2*H*)-furanones could also be prepared by following a similar strategy; this will be discussed in a later section.

5. Methods for the Synthesis of 5-Substituted-3(2*H*)-furanones

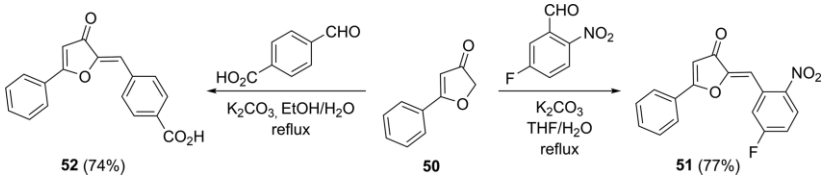
Suliman and co-workers reported the synthesis of 5-substituted-3(2*H*)-furanone starting from benzaldehyde (Scheme 10).[15] The synthetic route involving three steps commenced with the conversion of benzaldehyde to benzaldoxime **47** from which 3-phenyl-5-(isoxazolyl) methanol **48** was prepared by a 1,3-diploar cycloaddition with propargyl alcohol. The substituted isoxazole



Scheme 9. Synthesis of 4-substituted-3(2*H*)-furanones **45** from β-diketones.



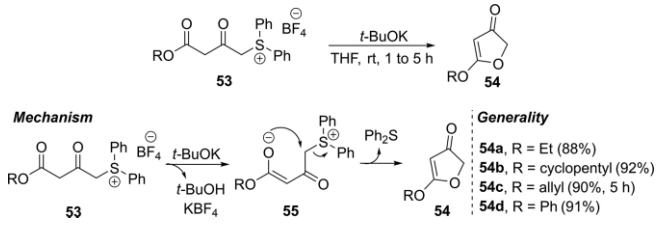
Scheme 10. Synthesis of 5-phenyl-3(2*H*)-furanone **50** from an isoxazole.



Scheme 11. Synthesis of 2,5-disubstituted-3(2*H*)-furanones from 5-substituted-3(2*H*)-furanone **50**.

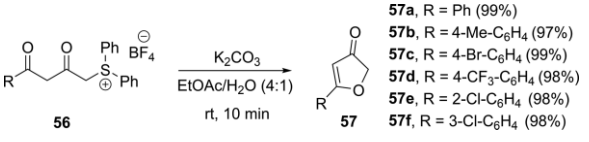
was subjected next to catalytic hydrogenation with 10 % Pd/C as catalyst and subsequent acidic hydrolysis furnished 5-phenyl-3(2*H*)-furanone **50** in 62 % yield. The authors used the 5-substituted-3(2*H*)-furanone for the synthesis of two fluorescent organic dyes (Scheme 11). 5-phenyl-3(2*H*)-furanone **50** was subjected to aldol condensation with 5-fluoro-2-nitrobenzaldehyde and 4-formylbenzoic acid to afford the corresponding products **51** and **52**, respectively. Detailed photophysical properties of these two fluorophores were evaluated and it was found that both dyes showed positive solvatochromic effects with increasing solvent polarity.

In 2016, the group of Kawano described an intramolecular cyclization of 3-alkoxycarbonyl-2-oxopropyldiphenyl sulfonium salts towards 5-substituted-3(2*H*)-furanones (Scheme 12).[16] Different sulfonium salts **53** were prepared by treating various substituted 4-bromo-acetoacetates with diphenyl sulfide in the presence of $AgBF_4$. These sulfonium salts were then allowed to undergo intramolecular cyclization in the presence of a base. Irrespective of the substituent on the ester functionality, the corresponding 5-substituted-3(2*H*)-furanones **54** were obtained in good to excellent yields after the base-mediated cyclization and all reactions were complete in an hour except the formation of 5-allyloxy-3(2*H*)-furanone **54c** which took 5 h to completion. The mechanism of the reaction starts with the formation of the enolate **55** from the sulfonium salt. The enolate oxygen then attacks the sulfur atom of the sulfonium moiety and thereby furnishes the expected 5-substituted-3(2*H*)-furanone with the elimination of dimethyl sulfide. In the same report the authors improved the method mentioned above to synthesize 4,5-disubstituted-3(2*H*)-furanones by including an alkylation step, which will be discussed in a later section.



Scheme 12. Synthesis of 5-substituted-3(2*H*)-furanones **54**.

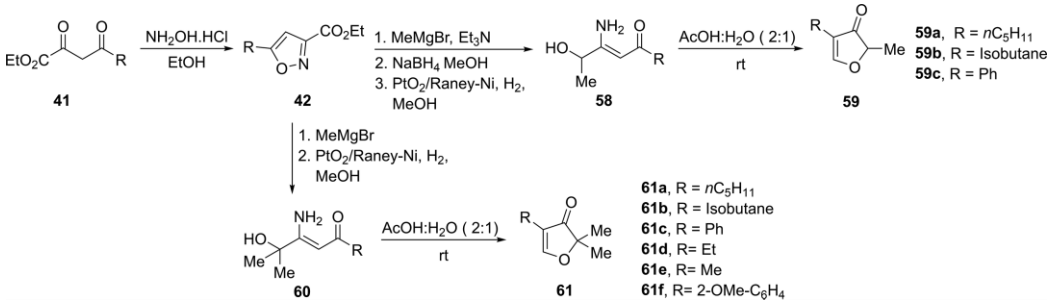
In 2018, the same authors reported the synthesis of 5-aryl-3(2*H*)-furanones by a similar strategy as described above (Scheme 13). In this report they utilized (4-aryl-2,4-dioxobutyl) methyl-phenylsulfonium salts **56** instead of acetoacetates as in the previous case.[17] These sulfonium salts **56** upon base induced intramolecular cyclization afforded 5-aryl-3(2*H*)-furanone **57** by a similar mechanism as discussed in the previous case. The starting (4-aryl-2,4-dioxobutyl) methylphenylsulfonium salts **56** were prepared from commercially available 1-arylethanones. The optimized condition for the intramolecular cyclization employed a combination of K_2CO_3 in a 4:1 mixture of EtOAc and H_2O at room temperature. Under these conditions the reaction was found to be general regardless of the substituent on the aryl ring affording the respective 5-aryl-3(2*H*)-furanones **57** in excellent yields.



Scheme 13. Synthesis of 5-aryl-3(2*H*)-furanones **57**.

6. Methods for the Synthesis of 2,4-Disubstituted-3(2*H*)-furanones

Simoni and co-workers also utilized ethyl-2,4-dioxoalkanoates as starting materials for synthesizing 2,4-disubstituted 3(*2H*)-furanones (Scheme 14).[14] As described earlier, the first step of the synthetic route involved the conversion of a β-diketone into 3,5-disubstituted isoxazoles **42**. Then the ester moiety of the isoxazoles was converted into a secondary or tertiary alcohol function by a two stage protocol. Its first step consisted in the reaction of the isoxazole with methylmagnesium iodide, and the second step was either reduction using sodium borohydride for secondary alcohols or hydrogenation with a PtO_2/Raney-Ni mixture for tertiary alcohols. The reduction product of the secondary alcohol was then hydrogenated to the β-enamino-ketone **58**. The amino ketones **58** and **60** were further subjected to acid catalysed cyclodehydration to generate the corresponding 3(*2H*)-furanones **59** and **61**, respectively. The au-



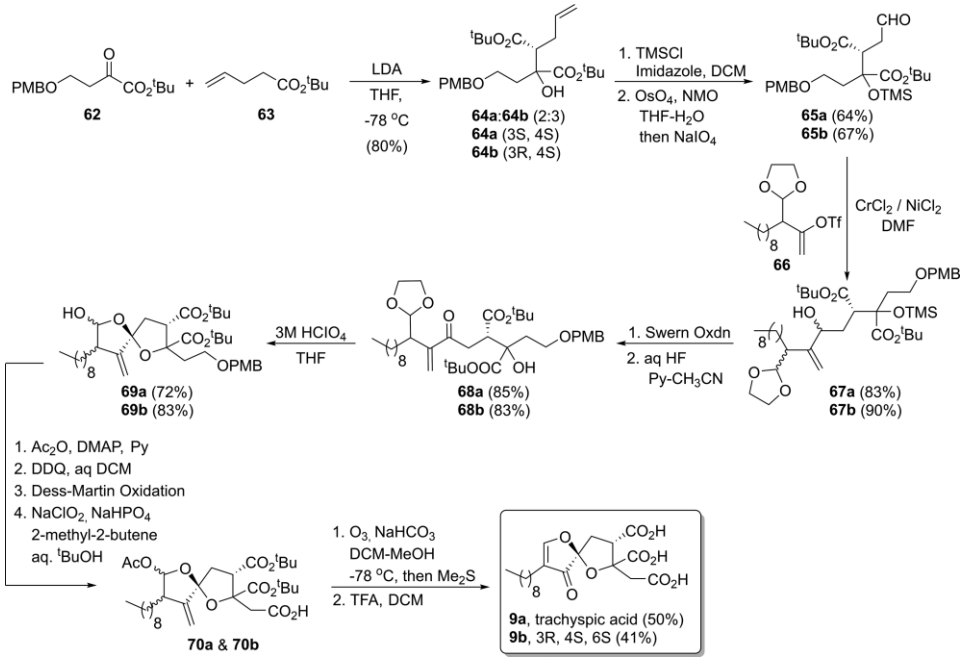
Scheme 14. Synthesis of 2,4-substituted-3(2*H*)-furanones **59** and **61** from β-diketones.

thors also reported on the synthesis of 3(*2H*)-furanimines from the tertiary alcohols **60** containing an enaminone functionality.

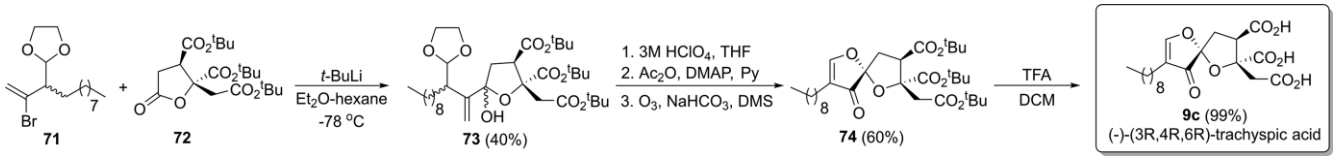
In 2003, Hatakeyama and co-workers reported on the total synthesis of (±)-trachyspic acid, a 2,4-disubstituted-3(2*H*)-furanone derivative (Scheme 15).[18] This spirocyclic natural product with heparanase inhibitory activity was isolated from the culture broth of *Talaromyces trachyspermus* SANK 12191. The synthesis of this spirocyclic-3(2*H*)-furanone starts with the aldol reaction of the α-keto ester **62** with the lithium enolate resulted from *tert*-butyl 4-pentenoate **63** which furnished a 2:3 mixture of aldol adducts **64a** (3S, 4S) and **64b** (3R, 4S). These isomers were further subjected to oxidative cleavage of the double bond to obtain a stereoisomeric mixture of aldehydes **65a** and **65b**.

A Cr(II)/Ni(II)-mediated Nozaki-Hiyama-Kishi coupling of these aldehydes with alkenyl triflate **66** provided the intermediate **67** which was further subjected to Swern oxidation, desilylation and acid mediated cyclization to generate the stereoisomeric mixture of spiroketals **69a** and **69b**. This was followed by transformations such as acetylation, PMB-deprotection and successive oxidations to generate the carboxylic acid intermediates **70a** and **70b**. Finally, ozonolysis followed by ester-deprotection furnished tricarboxylic acids **9a** and **9b**. The compound **9a** showed identical ^{1}H and ^{13}C NMR spectra with that of trachyspic acid; the relative stereochemistry of **9a** was established as 3*S*, 4*S* and 6*S*.

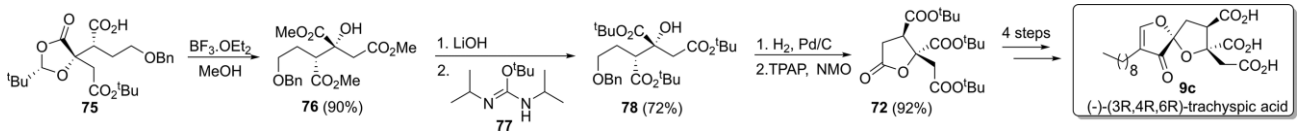
The enantiospecific total synthesis of (–)-trachyspic acid was reported later by Rizzacasa and co-workers (Scheme 16).[19] The first step involved the addition of the anion derived from vinyl bromide **71** to the chiral lactone **72**. The acetal **73** was then subjected to deprotection of the dioxolane part under acidic conditions which gave rise to ensuing spirocyclisation. Acetylation and subsequent ozonolysis and elimination in succession provided the spirocyclic 3(2*H*)-furanone **74** as a 4:1-mixture of diastereomers. The ultimate TFA induced deprotection of the ester functionalities furnished (–)-(3*R*, 4*R*, 6*R*)-trachyspic acid **9c**, which was identical with the natural product except for the opposite optical rotation. Thus, the authors could prove that the natural (+)-trachyspic acid has the absolute configuration of 3*R*, 4*S*, 6*S*; opposite to that of **9c**.



Scheme 15. Total synthesis of (±)-trachyspic acid **9**.



Scheme 16. Enantioselective total synthesis of (–)-trachyspic acid **9c**.



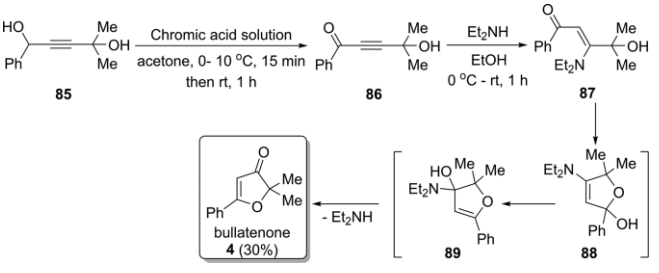
Scheme 17. Enantioselective total synthesis of (–)-trachyspic acid **9c**.

Another enantioselective total synthesis of the same molecule was reported by Barrett and co-workers in 2009, using Evans aldol reaction and Seebach dioxolanone alkylation reaction via Rizzacasa lactone **72** (Scheme 17).[20] The synthesis of the Rizzacasa lactone **72** was initiated by the ring-opening of dioxolanone **75** using BF_3•Et_2O in methanol under reflux conditions towards the triester intermediate **76** which upon LiOH mediated saponification followed by direct re-esterification towards tri-*tert*-butyl ester **78** using *N*,*N*′-diisopropyl-*O*-*tert*-butyl isourea **77**. Hydrogenolysis and tetra-propylammonium perruthenate (TPAP) oxidation provided the lactone **72** in an overall yield of 21 % in five steps. (–)-Trachyspic acid **9c** was synthesized in four steps using reported procedures from the lactone **72**.

Very recently Rafaniello and Rizzacasa extended their studies with the total synthesis of spirocyclic-3(2*H*)-furanone containing natural products and reported the total synthesis of (+)-trachyspic acid 19-*n*-butyl ester **84** isolated from the same fungal strain RKGS–F2684, from which trachyspic acid was isolated. The total synthesis starts with the formal [2+2]cycloaddition of silylketene acetal derived from (*S*)-(+)-γ-hydroxymethyl-γ-butyrolactone and di-*n*-butylacetylene dicarboxylate **79** (Scheme 18).[21] The cyclobutene diester **80** formed was transformed to aldehyde **81** by successive ring opening, rearrangement, orthogonal ester protection, silylation and oxidative cleavage of the alkene. Then the aldehyde **81** was subjected to Nozaki-Hiyama-Kishi coupling with vinyl iodide **82** followed by Swern oxidation to provide the enone **83** as a 1:1-mixture of diastereomers. An acid induced spiroacetal formation and acetylation followed by ozonolysis of this enone **83** afforded the desired 3(2*H*)-furanone-di-*tert*-butyl ester as the major spiroisomer (dr 6:1). Deprotection of this diester using TFA afforded the trachyspic acid 19-*n*-butyl ester **84** in excellent yield. The stereochemical outcome of the spirocyclization step was explained by the attack of the aldehyde at the oxonium ion intermediate from the less hindered *re*-face.

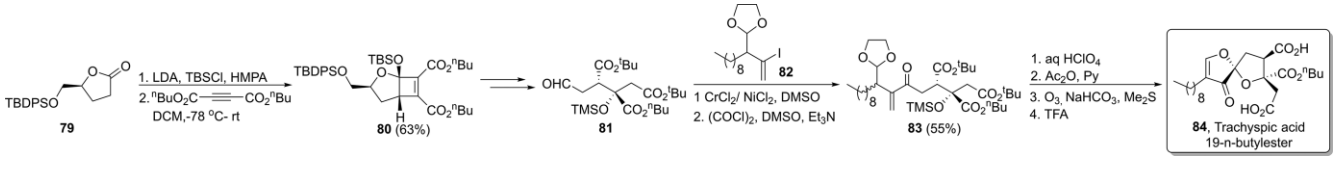
7. Methods for the Synthesis of 2,5-Disubstituted-3(2*H*)-furanones

The first report on the synthesis of 2,5-disubtituted-3(*2H*)-furanone came in 1958 from Raphael and co-workers. The structure of the natural product bullatenone **4** was confirmed by the authors by synthesizing it from 2-methylbut-3-yn-2-ol. The synthesis was initiated by the preparation of the acetylenic diol **85** by the addition of the Grignard reagent derived from 2-methylbut-3-yn-2-ol to benzaldehyde. The acetylenic diol **85** was then subjected to Jones oxidation to the corresponding hydroxy-ketone **86** followed by the addition of diethylamine to the acetylenic part to generate the enaminone **87**. Distillation of **87** was hypothesized to generate the cyclic tautomer **88** which upon oxotropic rearrangement gave a dihydrofuran intermediate **89** from which diethylamine was eliminated to yield bullatenone in 30 % yield (Scheme 19).[22]



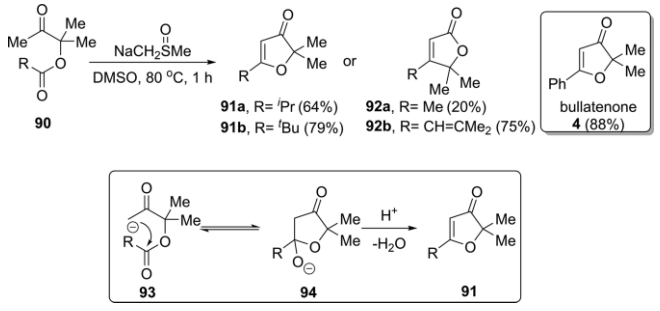
Scheme 19. Total synthesis of bullatenone **4**.

In 1965, Lehmann reported a sodium dimsyl mediated reaction of α-acyloxy ketone in DMSO from which a mixture of α-hydroxyfuranone and butenolide was found to form, the latter in major proportion.[23] Later, in 1981, Smith and co-workers studied the above mentioned transformation in detail using



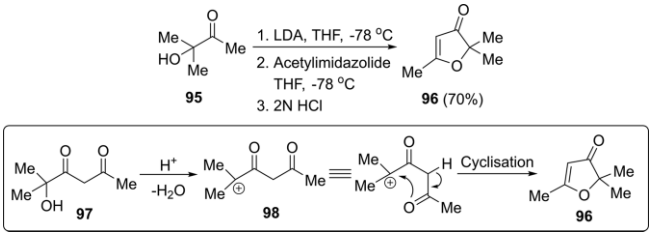
Scheme 18. Enantioselective total synthesis of trachyspic acid 19-*n*-butyl ester **84**.

α-acyloxy ketone **90** in such a way that 3(2*H*)-furanone was obtained as the sole product (Scheme 20).[24]



Scheme 20. Synthesis of 2,5-disubstituted-3(2*H*)-furanones **91** from α-acyloxy ketones.

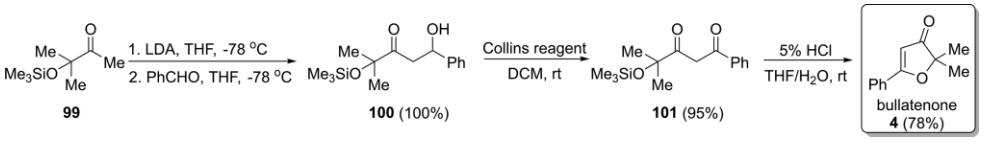
This was effected by modifying the α-acyloxy ketone moiety such that it holds no more than one hydrogen atom in the α′-position of the ester substituent. 3(*2H*)-furanones **91** were obtained in good to excellent yields when R was ^{i}Pr, Ph or ^{t}Bu substituents and butenolides **92** were formed as the sole products with R corresponding to Me or CH=CMe$_2$. Notably, by this methodology they could synthesize bullatenone (R = Ph) in excellent yields. The initial step of the reaction involved the generation of the anion **93** followed by intramolecular attack of this anion at the ester carbonyl group to afford the intermediate **94**. Dehydration of **94** finally furnished the 2,5-disubstituted-3(2*H*)-furanone **91.** The authors also discovered that substituted α′-hydroxy-1,3-diketone **97** could serve as the proper starting material for accessing 2,5-disubstituted-3(2*H*)-furanones (Scheme 21).[24] α′-hydroxy-1,3-diketone **97** was prepared by treating the dianion of α′-hydroxy-ketone **95** with suitable acylating agents. The acid catalyzed synthesis of 2,5-disubstituted-3(2*H*)-furanones from α′-hydroxy-1,3-diketones proceeds by a tandem dehydration-cyclization pathway.



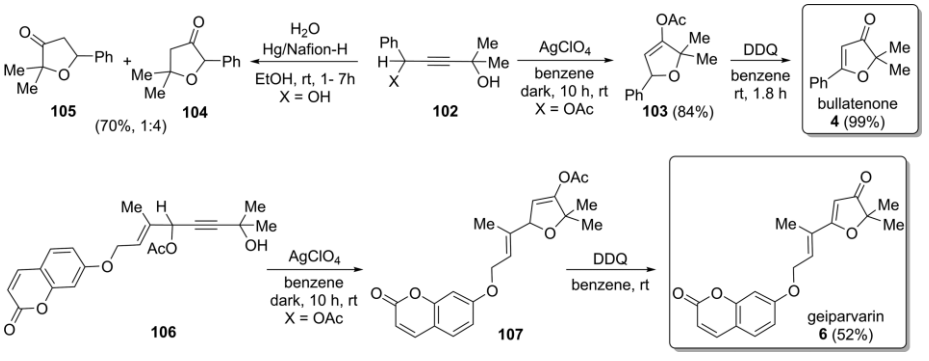
Scheme 21. Synthesis of 2,5-disubstituted-3(2*H*)-furanones **96** from α′-hydroxy-1,3-diketones.

Another synthetic route involving 3-steps towards 2,5-disubstituted-3(2*H*)-furanones was also devised by the same authors (Scheme 22).[24] This method starts with an aldol condensation of an aldehyde or ketone with an appropriately substituted (trimethylsilyl)oxybutan-2-one **99**. The aldol adduct **100** is subsequently oxidized to the corresponding (trimethylsilyl)oxy functionalized 1,3-diketone **101** which is finally subjected to an acid catalyzed dehydration-cyclization cascade to furnish 2,5-disubstituted-3(2*H*)-furanones such as **4**. The synthesized furanones were further subjected to synthetic transformations such as alkylation, conjugate addition of organocuprate reagents, and reaction with sulfur nucleophiles.

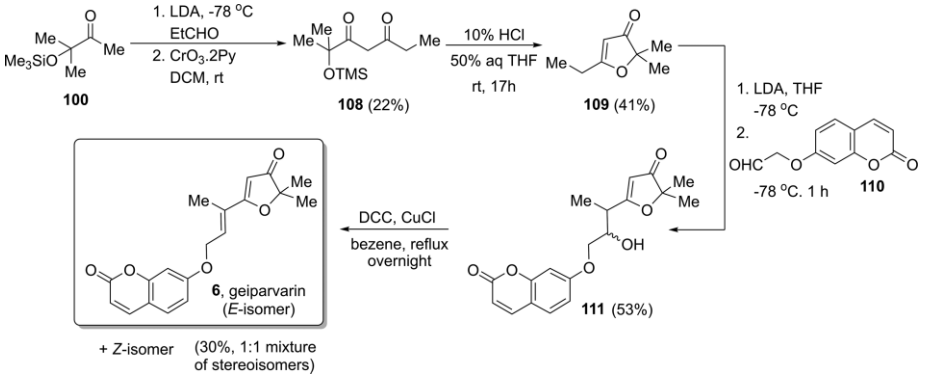
In the same year Hiyama and co-workers discussed a regiocontrolled hydration of 2-butyne-1,4-diol derivatives **102** for the synthesis of 4,5-dihydro-3(2*H*)-furanones (Scheme 23).[25] They applied this method for the synthesis of two 3(2*H*)-furanone containing natural products, bullatenone **4** and geiparvarin **6**. In this study they discussed a Ag(I)-catalyzed cyclization of monoacetylated unsymmetrical 2-butyne-1,4-diols to dihydro-3(*2H*)-furanone derivatives **103**. Oxidation of the resulting enol acetates **103** with dichlorodicyano-*p*-benzoquinone (DDQ) in benzene at room temperature yielded the corresponding 3(2*H*)-furanone derivatives quantitatively. In addition, the opposite regioisomers **104** and **105** were accessed by using a polymer



Scheme 22. Synthesis of 2,5-disubstituted-3(2*H*)-furanones from α′-(trimethylsilyloxy)-1,3-diketones **101**.



Scheme 23. Synthesis of 2,5-disubstituted-3(2*H*)-furanones from 2-butyne-1,4-diol derivatives.



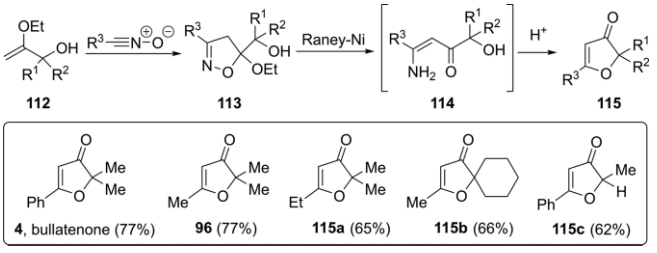
Scheme 24. Total synthesis of geiparvarin **6**.

reagent Hg/Nafion-H in EtOH. The Ag(I)-catalyzed cyclization of monoacetylated 2-butyne-1,4-diols and oxidation sequence was utilized for the synthesis of **4** and **6**.

The total synthesis of geiparvarin **6**, a natural product with antitumor properties was published by Jerris and Smith building on their previously developed methodology depicted in Scheme 24. The synthetic procedure involves the initial synthesis of two fragments, namely 2,2-dimethyl-5-ethyl-3(2*H*)-furanone **109** and 7-(2-oxoethoxy)coumarin **110**. The 3(2*H*)-furanone **109** was obtained by following the three-step route starting from 3-methyl-3-(trimethylsilyl)oxybutan-2-one. The two fragments **109** and **110** were then subjected to γ-aldol condensation followed by dehydration with DCC and CuCl. Both *E*- and *Z*-isomers were formed, and by using NMR experiments and X-ray crystal data they elucidated the configuration of geiparvarin (*E*-isomer) and its configurational isomer (Scheme 24).[26]

Another interesting approach of 2,5-disubstituted-3(2*H*)-furanones from isoxazolines was reported by Curran and Singleton (Scheme 25).[27] Their synthetic strategy started with the dipolar cycloaddition of nitrile oxides to enol ethers **112** to synthesize substituted isoxazolines **113**. These heterocycles upon Raney-Ni mediated reduction followed by acid catalysed cyclisation afforded the corresponding 2,5-disubstituted-3(2*H*)-furanones **115**. The authors extended the methodology to the synthesis of bullatenone **4**, which was obtained in 77 % yield.

In continuation of the work on the synthesis of substituted-3(2*H*)-furanones, Hiyama and co-workers utilized the Hg/Nafion-H chemistry with properly substituted propargylic alcohols **116** to produce different 2,5-disubstituted-3(2*H*)-furanones **115**. By following this protocol, bullatenone **4** was synthesized in quantitative yield from 4-hydroxy-4-methyl-1-phenylpent-2-yn-1-one. In the same report, yet another method for synthesizing

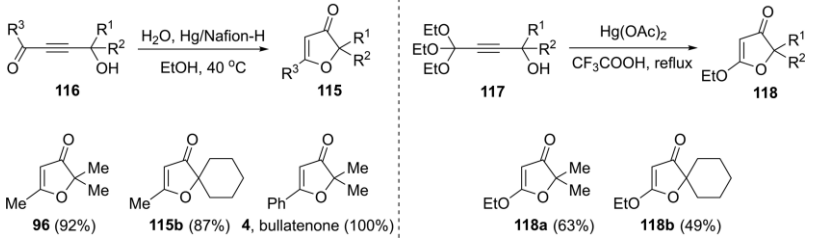


Scheme 25. Synthesis of 2,5-disubstituted-3(2*H*)-furanones from isoxazolines **113**.

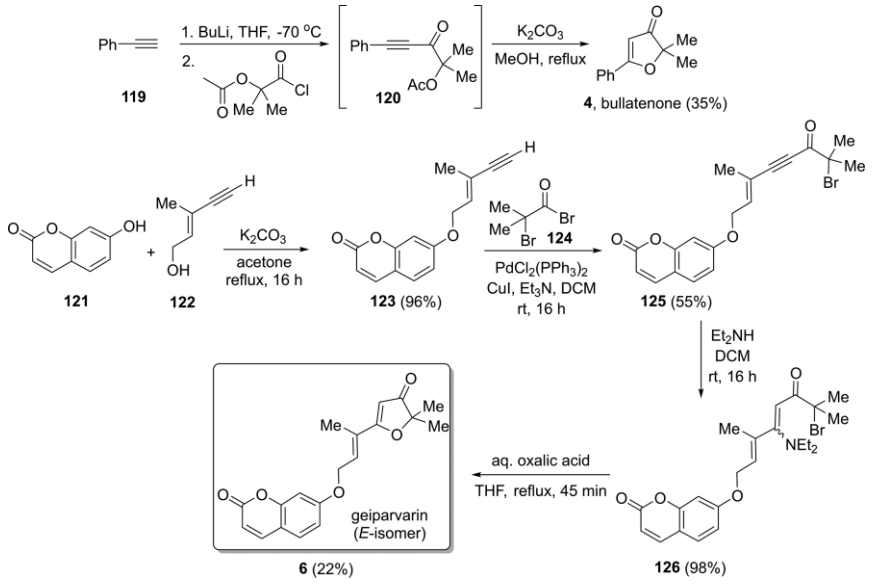
disubstituted-3(2*H*)-furanones **118** starting from functionalized 4,4,4-triethoxybut-2-yn-1-ol **117** was introduced. This transformation was performed in the presence of $Hg(OAc)_2$ and in refluxing CF_3COOH (Scheme 26).[28]

Jackson and Raphael in 1984 reported novel routes to bullatenone **4** and geiparvarin **6** (Scheme 27).[29] The synthesis of **4** started with the conversion of phenyl acetylene **119** to acetylenic ketone **120**. Refluxing **120** in the presence of K_2CO_3 in MeOH provided **4** in 35 % yield. In the case of **6**, the acetylenic coumarin **123** was prepared by treating 7-hydroxycoumarin **121** with (*E*)-3-methylpent-2-en-4-yn-1-ol **122**. The acetylenic bromoketone **125** was then synthesized from **123** by reacting 2-bromo-2-methylpropanoyl bromide **124** in a Pd(II)-Cu(I)-catalysed coupling process. The enaminone **126** generated from bromoketone **125** was finally converted to **6** by a hydrolysis followed by cyclisation.

Another interesting route towards 2,5-disubstituted-3(2*H*)-furanone appeared in 1985 which followed a mercuric acetate mediated oxidative cyclization of allenic ketones (Scheme 28).[30] The authors utilized the method for the synthe-

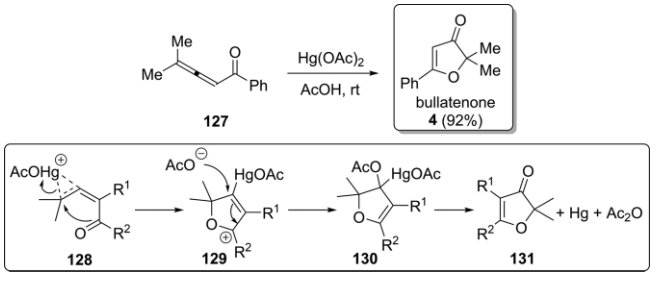


Scheme 26. Synthesis of 2,5-disubstituted-3(2*H*)-furanones from propargylic alcohols.



Scheme 27. Total syntheses of bullatenone **4** and geiparvarin **6**.

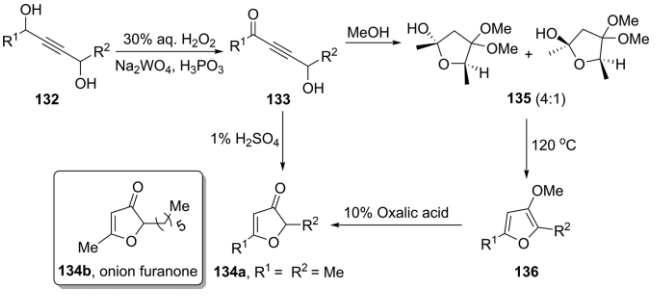
sis of **4** in 92 % yield. The initial step of the mechanism is the addition of the metal to the more electron-rich double bond of the allene **127** which is followed by cyclisation to afford the dihydrofuran intermediate **129**. The expected 2,5-disubstituted-3(2*H*)-furanone is generated after the attack of acetate ion along with the expulsion of mercury (metal) and acetic anhydride.



Scheme 28. Synthesis of 2,5-disubstituted-3(2*H*)-furanones from allenic ketones.

In 1986 Thomas and Damm reported on the synthesis of 2-hexyl-5-methyl-3(2*H*)-furanone **134b** otherwise known as "onion furanone" (Scheme 29).[31] The synthesis commences with the tungstate ion catalyzed oxidation of the acetylenic diol **132** with hydrogen peroxide. The obtained acetylenic hydroxy ketone **133** can next be readily converted to 2,5-disubstituted-3(2*H*)-furanone **134** by an acid catalyzed cyclization. The authors have also demonstrated a longer route towards disubstituted-3(2*H*)-furanones from **133** by the addition of methanol to the triple bond. The acetals **135** were then heated to 120 °C to furnish 3-methoxy-2,5-dimethylfuran **136** which upon treatment with aqueous oxalic acid furnished 2,5-disubstituted-3(2*H*)-furanones **134**.

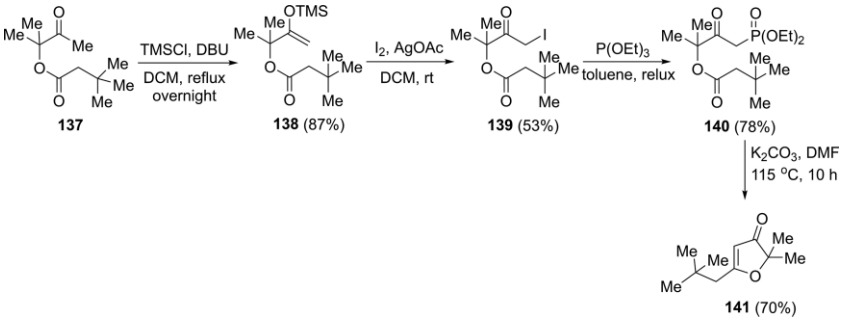
Weimer and co-workers introduced a new strategy for the synthesis of 2,5-disubstituted-3(2*H*)-furanones by an intramolecular Horner-Wadsworth-Emmons-type condensation (Scheme 30).[32] The synthetic route started from the keto ester



Scheme 29. Synthesis of 2,5-disubstituted-3(2*H*)-furanones from acetylenic diols.

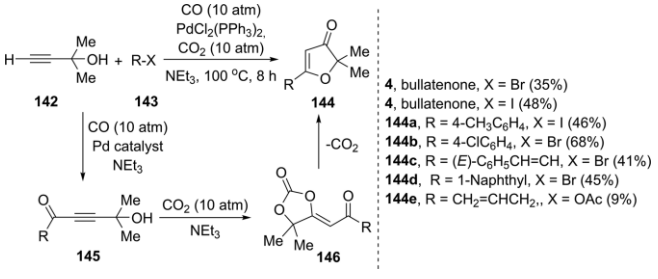
137 which on treatment with TMSCl and DBU in refluxing DCM afforded the corresponding silyl enol ether **138**. Iodination of **138** followed by an Arbuzov reaction of the α-iodo keto ester **139** provided the β-ketophosphonate **140**. The final condensation of **140** was effected by treating these intermediates with K_2CO_3 in DMF to yield 2,5-disubstituted-3(2*H*)-furanone **141**.

In 1989 Inoue and co-workers reported a facile method for the synthesis of 2,5-disubstituted 3(2*H*)-furanones from propargylic alcohols **142**, CO and organic halides **143** using transition metal catalysis under an atmosphere of CO_2 (Scheme 31).[33] The methodology was utilized for the synthesis of differently disubstituted 3(2*H*)-furanones **144** in moderate yields by changing the substituent at C-5 position. They synthesized bullatenone **4** from 2-methyl-3-butyn-2-ol, CO and a phenyl halide RX. The reaction is believed to proceed via the initial formation of a acetylenic ketone intermediate **145** which after conversion into a cyclic carbonate **146** undergoes a decarboxylative transformation to furnish the desired 2,5-disubstituted 3(2*H*)-furanone. Soon afterwards the same group utilized the same methodology for accessing 2,5-disubstituted-3(2*H*)-furanone containing natural products from α-ethynyl tertiary alcohols **147** (Scheme 32).[34] This procedure also involves the use of CO_2 which reacts with the α-ethynyl tertiary alcohol **147**



Scheme 30. Synthesis of 2,5-disubstituted-3(2*H*)-furanone **141** by an intramolecular Horner-Wadsworth-Emmons condensation.

to furnish the intermediate α-methylene cyclic carbonates **148** which subsequently fragment to the disubstituted-3(2*H*)-furanone **149**. By utilizing this methodology, the authors synthesized the antitumor natural product geiparvarin **6** and the flavoring compound 2,5-dimethyl-3(2*H*)-furanone **134a** in a one-pot process.

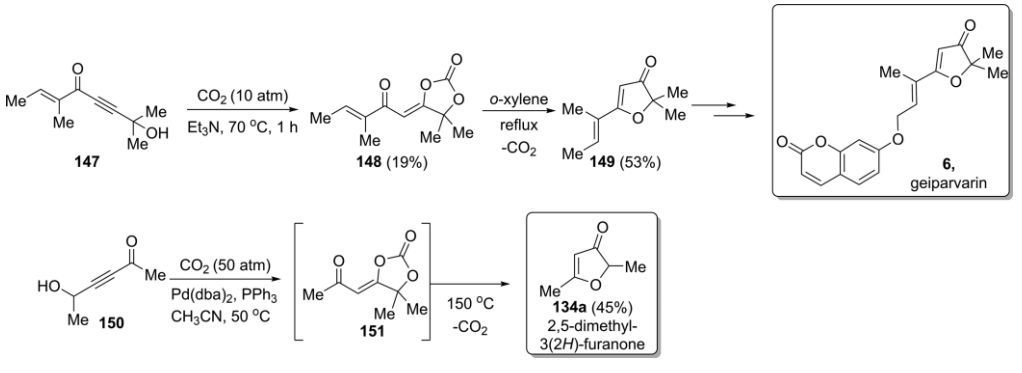


Scheme 31. Pd-catalyzed CO_2 mediated synthesis of 2,5-disubstituted-3(*2H*)-furanosnes **144**.

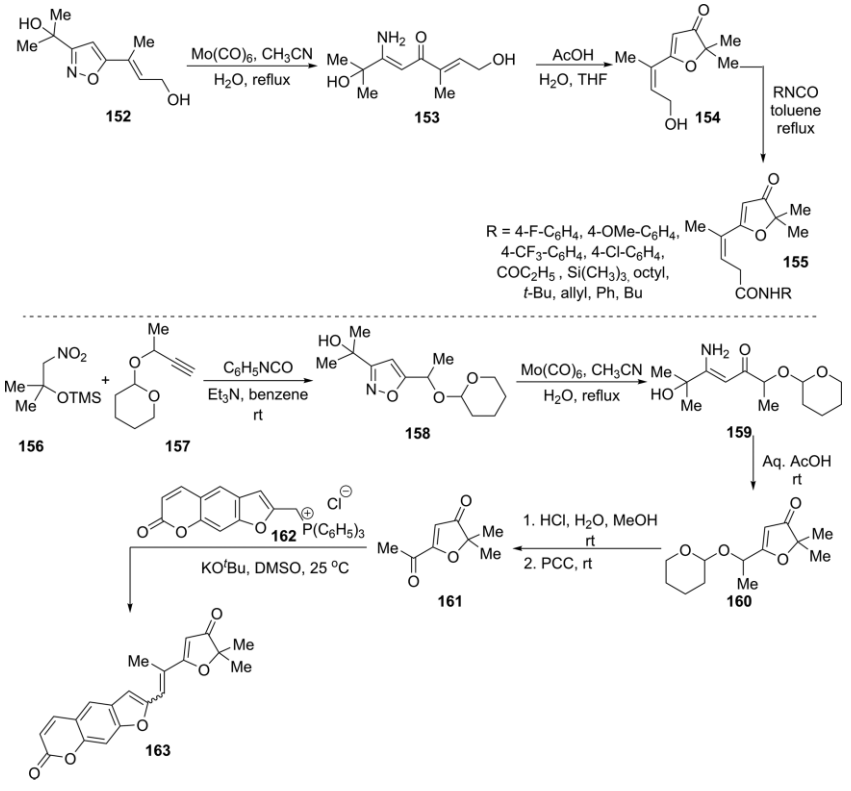
In 1994, Manfredini et al. presented the synthesis and cytostatic activity of geiparvarin analogues having a carbamate moiety on the alkyl side chain at C-5 of the 3(*2H*)-furanone ring.[35] In addition, they also prepared analogues of geiparvarin with a furocoumarin moiety attached to the side chain rather than a coumarin ring (Scheme 33).[35] The synthetic strategy started with the synthesis of an isoxazole ring **152** by a [3+2] cycloaddition of an alkyne to a nitrile oxide. The resulting isoxazole **152** was then refluxed in the presence of $Mo(CO)_6$ in wet CH_3CN to generate 3-enaminones **153**. The 3(*2H*)-furanone core of **154** was next synthesized by an acid-catalyzed cyclodehydration of the enaminones **153**. Finally, the hydroxyl group on the side chain of the furanone was allowed to react with different isocyanates in toluene at reflux condition to afford substituted carbamates **155**. The synthesis of furocoumarin attached geiparvarin analogues also followed the same synthetic strategy to the enaminones **159**. The THP-protected enaminone was then subjected to a two-step transformation involving the removal of the THP group and oxidation of the resultant hydroxyl group to the corresponding carbonyl function. The furocoumarin functionalized 3(*2H*)-furanone **163** was finally prepared from the 5-acetyl-3(*2H*)-furanone **161** by a Wittig reaction with the phosphonium salt **162**. All these compounds were tested for cytostatic activity against proliferation of murine and human tumor cells and were found to show promising results.

Villemin et al. reported a facile synthesis bullatenone and geiparvarin from the esters of 3-hydroxy-3-methylbutan-2-one **164** by an intramolecular cyclisation catalysed by cesium fluoride (Scheme 34).[36] The 3(*2H*)-furanone ring forms by a Knoevenagel condensation at the carbonyl group of esters of 3-hydroxy-3-methylbutan-2-one **164**. Bullatenone was synthesized from 2-methyl-3-oxobutan-2-yl benzoate by treatment with cesium fluoride at 300 °C in 70 % yield. Geiparvarin precursor **149** was synthesized in a comparable way. The 3(*2H*)-furanone **149** could easily be converted to geiparvarin by a two-step process.

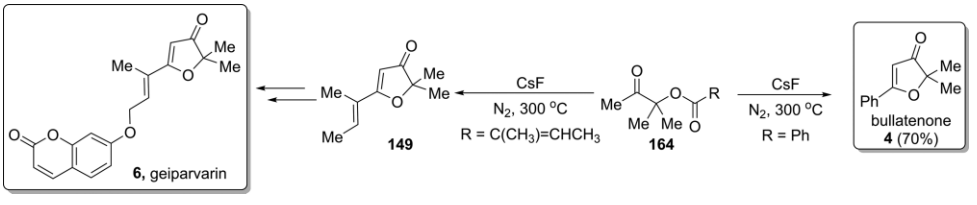
Another synthetic strategy for accessing 2,5-disubstituted-3(*2H*)-furanones via isoxazole intermediates was reported by Chimichi and co-workers (Scheme 35).[37] Functionalized isoxazolyl alcohols **167** were obtained by [3+2]cycloaddition of nitrile oxides **165** to alkynols **166**. On the other hand, isoxazoles were also prepared by a 3-step route involving a cycloaddition



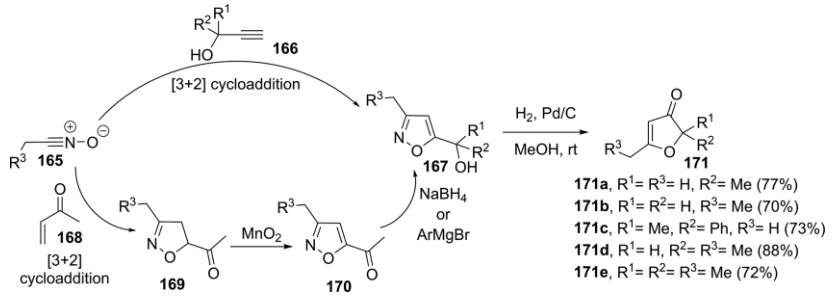
Scheme 32. CO_2 mediated synthesis of 2,5-disubstituted-3(*2H*)-furanones.



Scheme 33. Synthesis and derivatisation of geiparvarin analogues.



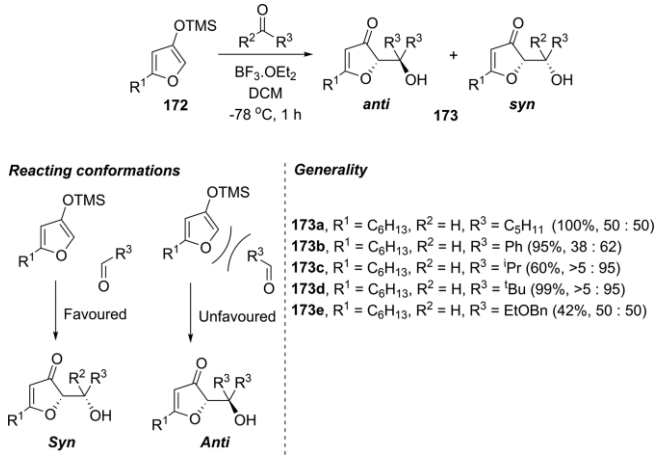
Scheme 34. Synthesis of 2,5-disubstituted-3(2*H*)-furanones by a CsF-catalyzed intramolecular cyclization.



Scheme 35. Synthesis of 2,5-disubstituted-3(2*H*)-furanones via isoxazole intermediates.

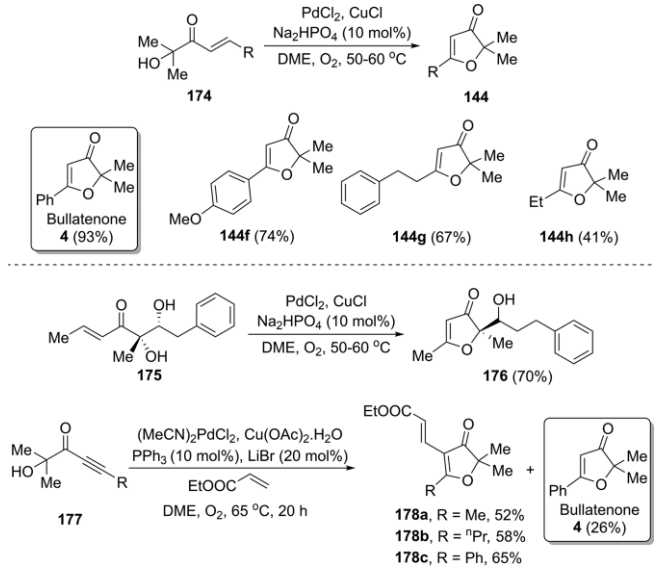
of nitrile oxide **165** with alkyl vinyl ketone **168** under Mukaiyama conditions followed by oxidation of the isoxazoline moiety **169** and final reduction of the carbonyl function in **170**. These isoxazoles **167** were then hydrogenated in the presence of a Pd/C catalyst in MeOH at room temperature by which 2,5-disubstituted-3(2*H*)-furanones **171** were obtained in good yields.

An interesting Lewis acid catalyzed stereoselective aldol reaction of 3-silyloxyfurans **172** with aldehydes for the synthesis of 2,5-disubstituted-3(2*H*)-furanones has been reported by Winkler and co-workers (Scheme 36).[38] An increase in the diastereoselectivity of the aldol reaction was noted with increasing steric hindrance of the aldehyde. In this line, it was found that the reactions with isobutyraldehyde and pivaldehyde showed a higher diastereoselectivity, whereas sterically unhindered aldehydes such as *n*-hexanal resulted only in modest diastereoselectivity. The observed diastereoselectivity is due to the aldol reaction that proceeds via the conformer which is sterically unhindered.



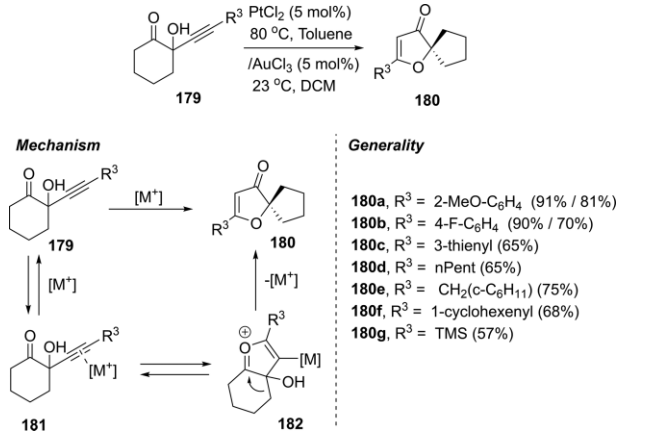
Scheme 36. Aldol reaction of 3-silyloxyfuran **172** with carbonyl electrophiles.

Another interesting approach towards 2,5-disubstituted-3(2*H*)-furanones from α-hydroxyenones and α, β-dihydroxyenones was reported by Gouverneur and co-workers in 2005 exploiting a palladium-catalyzed oxidative cyclization process (Scheme 37).[39] When β-hydroxy enones are subjected to the same oxidative cyclization process, an intramolecular oxidative conjugate addition leads to dihydropyranones. But with α-hydroxyenones **174** and α, β-dihydroxyenones **175** the catalytic 5-*endo* oxidative heterocyclization is the only reaction pathway. The same group extended their study to α-hydroxyynones **177** also, to prepare the 2,4,5-trisubstituted 3(*2H*)-furanones **178**. They found that bullatenone was formed as a side product with a phenyl-substituted alkyne substrate via a 5-*endo-dig* process.



Scheme 37. Palladium-catalyzed oxidative cyclization process for the synthesis of 3(*2H*)-furanones.

A synthetic route leading to spirocyclic 3(2*H*)-furanones was introduced by Kirsch and co-workers in 2006.[40] The methodology involved either a Au(III) or a Pt(II) catalyzed domino reaction for the synthesis of the 2,5-disubstituted-3(*2H*)-furanone. The reaction proceeded via transition metal catalyzed activation of the alkyne functionality in the starting 2-hydroxy-2-alkynyl carbonyl compounds **179** followed by a heterocyclization (to form **182**) and 1,2-migration. It was found that the reactions catalyzed by Au(III) salts provided higher yields but were restricted to aryl substituents. In contrast, Pt(II) salts catalyzed the domino reactions with substrates bearing both alkyl and aryl substituents. This approach to spirocyclic compounds is not only limited to forming five-membered spirocyclic ring systems but also applicable to cycloheptanone and cyclooctanone, which undergo ring contraction to give the corresponding (cyclohexyl and cycloheptyl) spirocycles. Furthermore, acyclic systems also reacted by migration of alkyl and aryl groups (Scheme 38).

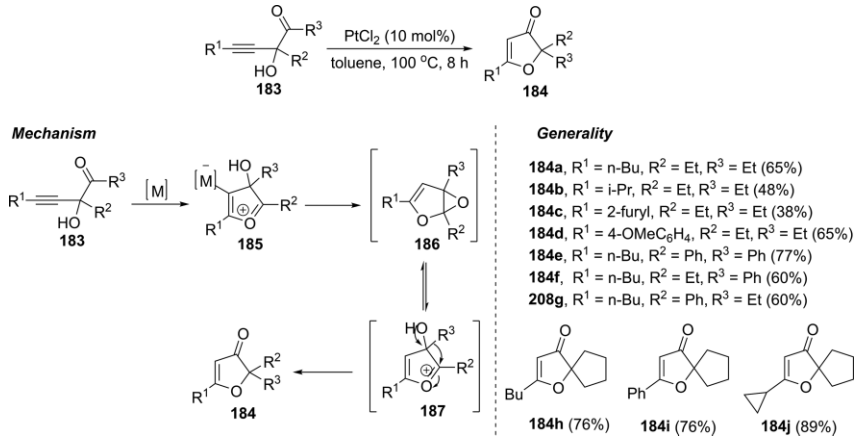


Scheme 38. Transition metal-catalyzed synthesis of spirocyclic-3(2*H*)-furanones **180**.

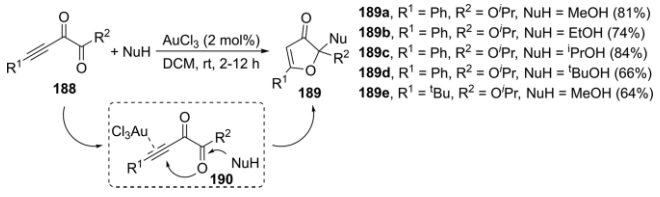
Another Pt-catalyzed cyclization strategy for the synthesis of 2,5-disubstituted-3(*2H*)-furanones from propargyl alcohols was reported in 2008.[41] The reaction was well tolerated by different substituted propargyl alcohols **183** from which the corresponding furanones were obtained in moderate to good yields. The authors could also make spirocyclic-furanones by starting from appropriate cyclic substrates. The reaction proceeds via the initial formation of a metallated zwitter ion **185** which is converted into an epoxide **186**. The epoxide ring opens up along with the migration of substituents to the 2nd position furnishing 2,5-disubstituted-3(*2H*)-furanones **184** (Scheme 39).

Another Au(III)-catalyzed synthesis 2,5-disubstituted-3(2*H*)-furanones was reported by the group of Liu in the same year (Scheme 40).[42] The synthesis was effected by a gold-catalyzed cyclization of 2-oxo-3-butynoic esters **188** and related compounds with a variety of nucleophiles. The reaction starts by the activation of the alkyne functionality (as shown in intermediate **190**) by the gold catalyst. This is followed by a domino nucleophilic attack/*anti-endo-dig* cyclization and finally a protonolysis to afford 2,5-disubstituted-3(2*H*)-furanone. The reaction was found to be general for a range of alkynes bearing aromatic as well as alkyl substituents, with different alcohols as nucleophiles, furnishing the cyclization products in good to excellent yields.

In 2006, the 5-methyl-3(*2H*)-furanone derivative or inotilone **5** was isolated and characterized by Wangun and co-workers from the fruiting body of the mushroom *Inonotus sp.*[43] This



Scheme 39. Pt-catalyzed synthesis of 2,5-disubstituted-3(*2H*)-furanones.

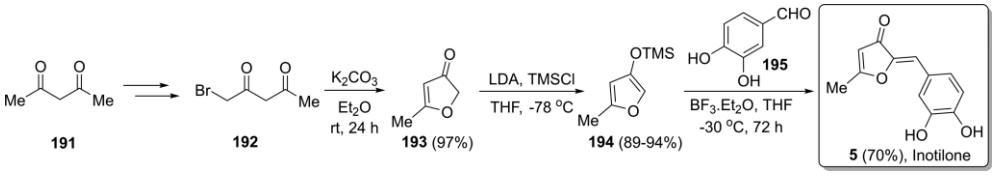


Scheme 40. Au(III)-catalyzed construction of 2,5-disubstituted-3(*2H*)-furanones **189** from activated alkynes.

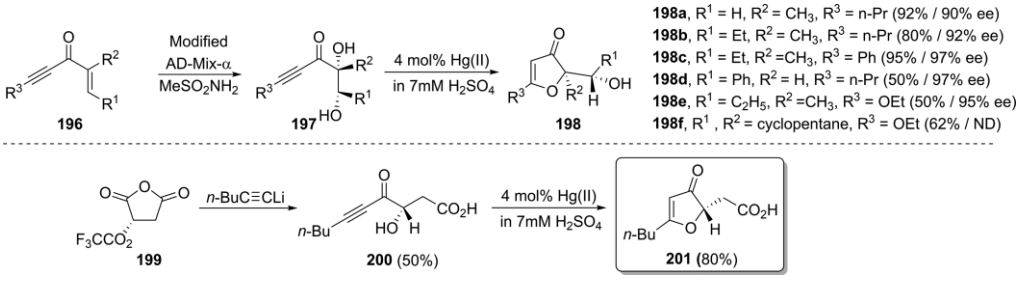
molecule was evaluated for its biological properties and was found to exhibit potent cyclooxygenase (COX) and xanthone oxidase (XO) inhibitory activities. This 2,5-disubstituted-3(*2H*)-furanone natural product was first synthesized in 2007 by Shamshina and Snowden in six steps and in 50 % overall yield.[44] The total synthesis started by the selective bromination of 2,4-pentanedione **191** to access 1-bromopentane-2,4-dione **192**. 5-methyl-3(*2H*)-furanone **193** was synthesized in 97 % yield from **192** by a base induced intramolecular nucleophilic substitution. The furanone **193** was then converted into the trimethylsilyloxyfuran **194** which was finally subjected to Mukaiyama aldol reaction conditions with 3,4-dihydroxy benzaldehyde **195** to afford inotilone **5** in 70 % yield (Scheme 41).

A catalytic asymmetric approach for the enantioselective synthesis of 2,5-disubstituted-3(*2H*)-furanones from enynones was developed by Marson et al. in 2007 (Scheme 42).[45] The first step of this sequence involves the asymmetric dihydroxylation of enynones **196** by Sharpless oxidation using a modified AD-mix-α containing 5 mol-% of $(DHQ)_2PHAL$ and 1 mol-% of $K_2[OsO_2(OH)_4]$. These dihydroxylated compounds **197** were then subjected to Hg(II)-catalyzed conditions to furnish 2,5-disubstituted-3(2*H*)-furanones **198** in high enantioselectivities. It was found that for the enynones which contained a terminal alkoxy group, the corresponding 2,5-disubstituted-3(2*H*)-furanone was formed after the step itself. The authors also utilized their approach to synthesize the natural product **201,** a known germination inhibitor.

In 2013, the same group used their methodology for the synthesis of the zaragozic acid core which is basically a 2,5-disubstituted-3(2*H*)-furanone moiety (Scheme 43).[46] In this

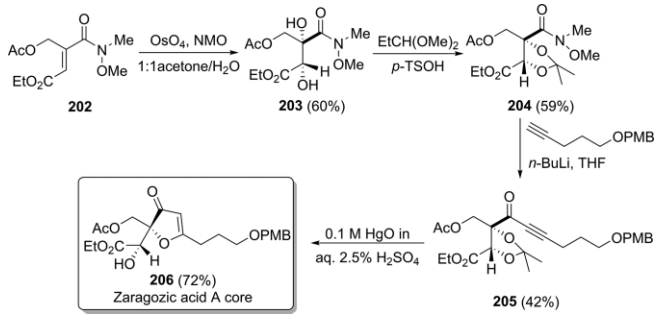


Scheme 41. Total synthesis of inotilone **5** from 2,4-pentanedione **191**.



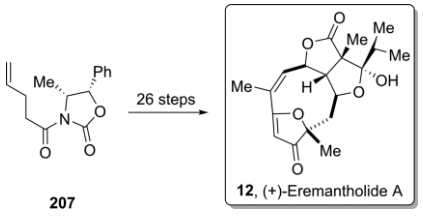
Scheme 42. A catalytic asymmetric approach for the synthesis of 2,5-disubstituted-3(2*H*)-furanones.

work, they first performed a dihydroxylation of the enone functionality in the Weinreb amide **202** and subsequently protected the 1,2-diol **203** as an acetal **204**. Then addition of alkynyl anion to the Weinreb amide generated the ynone **205** which was finally subjected to deprotection and cyclisation in one-pot in the presence of catalytic quantities of Hg(II) and sulfuric acid to afford zaragozic acid core **206** in 70 % yield.



Scheme 43. Synthesis of the zaragozic acid core.

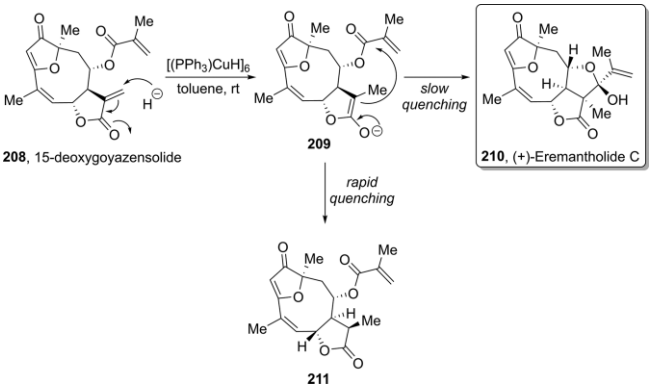
(+)-Eremantholide A **12** is a sesquiterpenoid containing a 2,5-disubstituted-3(*2H*)-furanone core which was isolated from *Eremanthus elaeagnus* in 1975 by Le Quesne and Brennan. The asymmetric total synthesis of this natural product was reported by Li and Hale. Their synthetic strategy consisted of 26 steps to (+)-eremantholide A from a commercially available chiral auxiliary **207**. The 3(*2H*)-furanone core unit present in the natural product was synthesized by following Chimichi's synthetic methodology (Scheme 44).[47] Biological evaluation of **12** revealed it is effective against human KB nasopharyngeal carcinoma.



Scheme 44. Total synthesis of (+)-eremantholide A **12**.

Constantino and co-workers demonstrated that furanoheliangolides could be converted into eremantholides by a one-step biomimetic transformation (Scheme 45).[48] They treated 15-deoxygoyazensolide **208** with Stryker's reagent in toluene at room temperature., affording a mixture of eremantholide C and **211**. This biomimetic process starts with the conjugate addition of hydride to the α-methylenic group in the lactone to furnish the enolate intermediate **209**. Carbanion generated from this enolate intermediate added to the ester carbonyl group of the same molecule to furnish eremantholide C. Fast quenching of the reaction (in 5 h) resulted in a mixture of eremantholide C and **211** in a ratio of 4:5, respectively. Whereas slow quenching of the reaction resulted in the predominant formation of eremantholide C.

In 2008, Nicolaou and co-workers presented the total synthesis of biyouyanagin A and analogues, dihydro derivatives of 3(*2H*)-furanone.[49] The total synthesis proceeded via a 3(*2H*)-

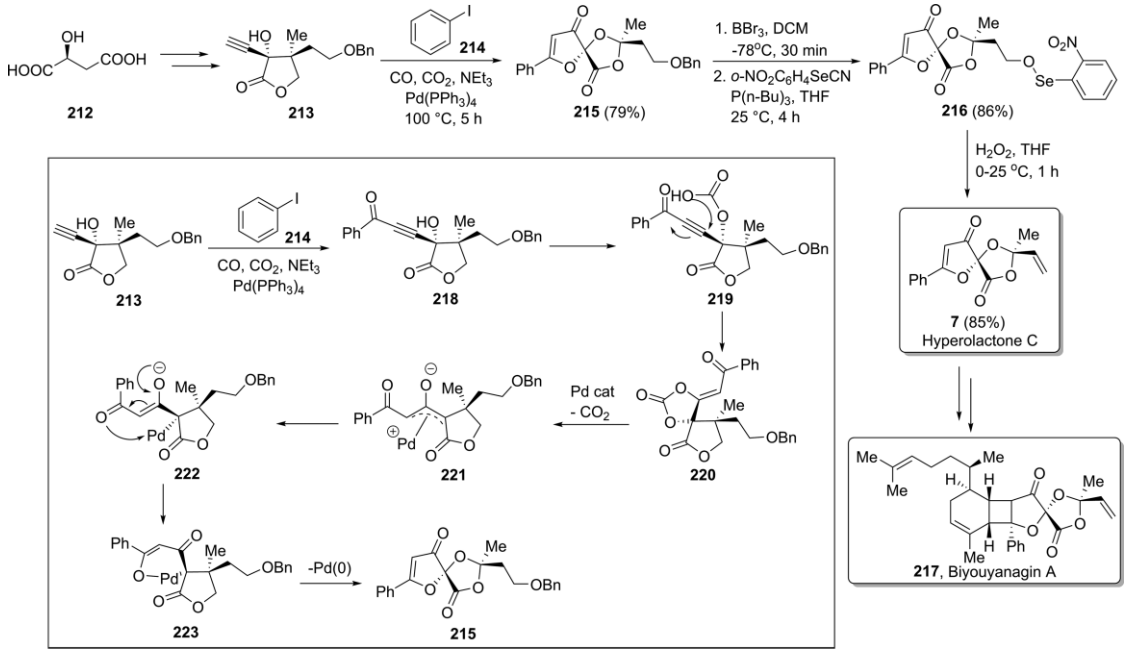


Scheme 45. Conversion of furanoheliangolide into eremantholide C **210**.

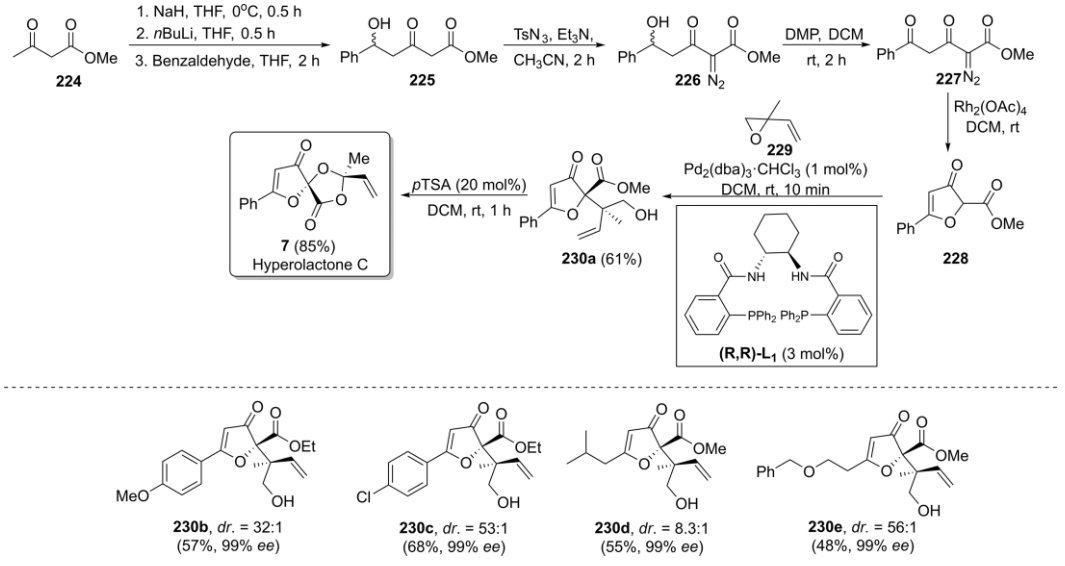
furanone moiety called hyperolactone C as the key building block. The synthesis of hyperolactone C started from (*S*)-malic acid **212** which in a 5-step synthetic transformation afforded the lactone **213** which was further subjected to a Sonogashira-type coupling reaction. This Pd-catalyzed reaction follows a cascade sequence with the initial formation of the acetylenic ketone **218** which takes up a molecule of CO_2 to form the intermediate **219**. Cyclization of the carbonic acid moiety in **219** leads to the formation of the cyclic carbonate **220** from which a π-allyl Pd complex **221** was formed by the extrusion of CO_2. Rearrangement occurs in intermediate **222** giving rise to the palladacycle **223** from which Pd(0) is expelled to yield the spirolactone intermediate **215**. 4-*epi*-Hyperolactone C was also synthesized by following the same strategy. The spirolactone intermediate **215** was converted into hyperolactone C **7** in 3 steps in an overall yield of 73 % (Scheme 46). Anti-HIV evaluation of biyouyanagin A, hyperolactone C and their derivatives revealed that the activity of biyouyanagin A most likely resides in hyperolactone C. Biyouyanagin A exhibited significant activityagainst HIV-1 replication with an IC_{50} value of 26 μM while the *para*-methoxy hyperolactone C derivative displayed an activity of 12 μM.

Soon afterwards, Xie and co-workers revealed another approach for the total synthesis of hyperolactone C and (–)-biyouyanagin A.[50] They adopted a Pd-catalyzed asymmetric allylic alkylation, lactonisation, photoinduced [2+2]cycloaddition pathway for the total synthesis (Scheme 47). This was initiated with the synthesis of β-keto ester **225** from benzaldehyde and methyl acetoacetate **224**. This was converted into α-diazo-β-keto ester **226** which upon further oxidation and rhodium catalyzed ring closure gave the 2,5-disubstituted 3(*2H*)furanone **228**. This furanone intermediate was subsequently subjected to a Pd-catalysed asymmetric allylic alkylation to construct the key vicinal quaternary carbon stereocenters. The ligand (R,R)-L_2 improved the diastereoselectivity to 26:1 and the enantioselectivity to 99 % *ee*, from 8.7:1 and 95 % *ee* when (R,R)-L_1 was used.

By varying the substituents on the β-keto esters the authors synthesized different substituted 2,5-disubstituted-3(*2H*)furanones **230a**–**230e** via a Pd-catalyzed asymmetric allylic alkylation with catalyst (R,R)-L_2. The precursor for ent-hyperolactone C was also prepared by the same protocol using (S,S)-L_2 as the catalyst. Product **230a** was unstable at room temperature and



Scheme 46. Total synthesis of hyperolactone C **7**.

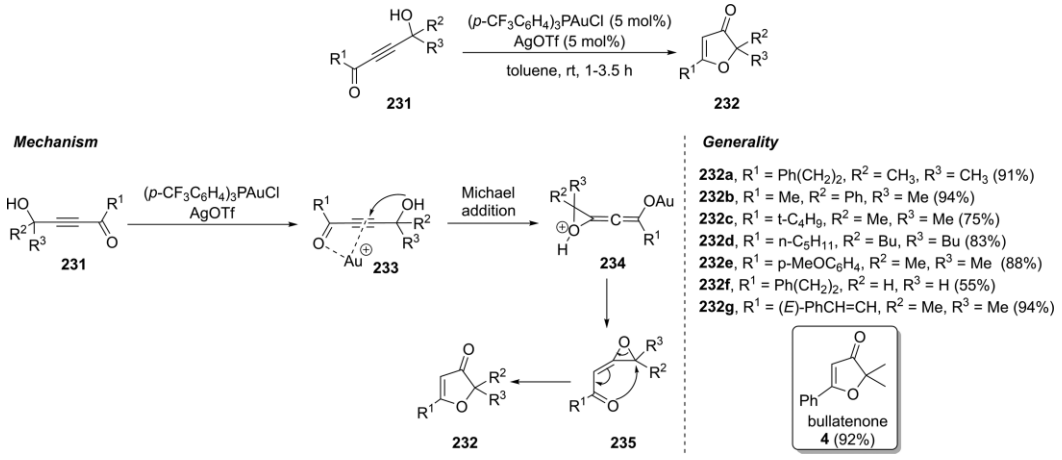


Scheme 47. Total synthesis of hyperolactone C **7**.

slowly was converted to hyperolactone C. This lactonisation was considerably enhanced by the addition of *p*TSA in catalytic amounts and hyperolactone C was generated with a *dr.* of 26:1 in 85 % yield after 1 hour. The final step consisted in a [2+2]cycloaddition of *ent*-zingiberene and hyperolactone C which provided (–)-biyouyanagin A **217** in an overall yield of 8 % within 7 steps. The authors also reported the synthesis of the unnatural enantiomer of (+)-biyouyanagin A by a [2+2]cycloaddition of ent-hyperolactone C and zingiberene.

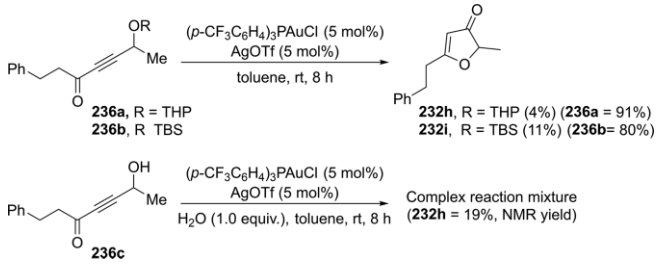
In 2010, a Au(I)/Ag(I) catalyzed intramolecular cyclization of γ-hydroxyalkynones to 2,5-disubstituted-3(*2H*)-furanone was reported (Scheme 48).[51] This method was general for the synthesis of a class of substituted 3(*2H*)-furanones **232** irrespective of the substituents present on the γ-hydroxyalkynones. The reaction is initiated by the coordination of the gold species to the π-bond of **231** followed by Michael addition of the hydroxyl group. The epoxide intermediate **234** formed then cyclizes via a nucleophilic attack of the carbonyl oxygen atom, giving rise to a 2,5-disubstituted-3(*2H*)-furanone. By utilizing this methodology, the Japanese authors synthesized bullatenone **4** in 92 % yield from a suitably substituted γ-hydroxyalkynone.

The formation of the epoxide as intermediate was further supported by the control experiments depicted in Scheme 49.[51] Similar reactions with protected derivatives **236a** and **236b** gave only trace amounts of the furanone. In the second experiment, the authors observed that addition of water as



Scheme 48. Au(I)-catalyzed synthesis of 2,5-disubstituted-3(*2H*)-furanones **232**.

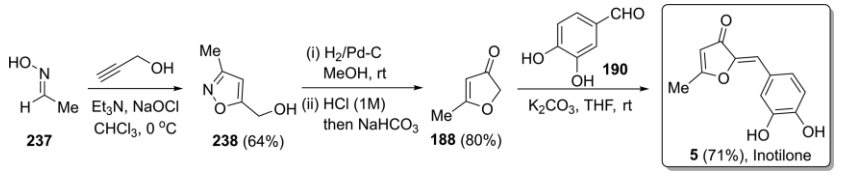
an external nucleophile inhibited the intramolecular cyclization step and they thus concluded that furanone formation was occurring via an epoxide intermediate (Scheme 49).



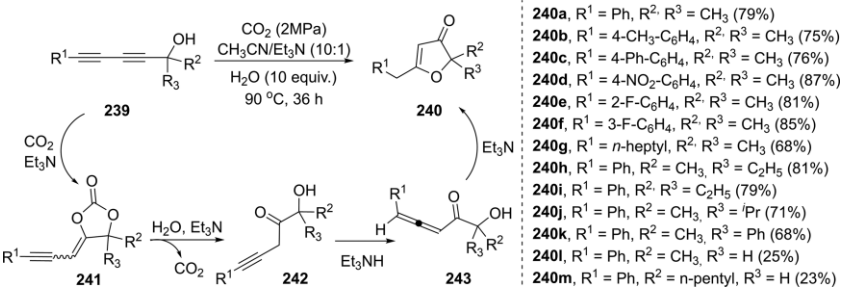
Scheme 49. Control experiments to support the mechanism of Au(I)-catalyzed synthesis of 2,5-disubstituted-3(*2H*)-furanones.

Later in 2010, an efficient 3 step route of inotilone **5** with 36 % overall yield starting from acetaldoxime was reported by Al-Busafi et al.[52] The authors started with the synthesis of the isoxazole **238** by a [3+2]dipolar cycloaddition of in situ generated nitrile oxide and propargyl alcohol. The isoxazole **238** was then subjected to a two-step process to synthesize the crucial intermediate 5-methyl-3(2*H*)-furanone **188** in 80 % yield. Aldol condensation of **188** with 3,4-dihydroxy benzaldehyde **190** resulted in the formation of inotilone **5** in 71 % yield (Scheme 50).

Another metal-free CO_2-mediated synthesis of 2,5-disubstituted-3(2*H*)-furanones from diyne alcohols was reported in 2011 (Scheme 51).[53] The conversion of the diyne alcohol **239** was carried out with 2MPa of CO_2 in the presence of 10 equiv. of H_2O and in a 10:1 mixture of CH_3CN/Et_3N at 90 °C for 36 h. The reaction was found to be general for a range of diyne alcohols with either alkyl or aryl substituents resulting in the corresponding disubstituted 3(2*H*)-furanones in good to excellent yields. The reaction proceeds by the initial base catalyzed formation of a cyclic carbonate **241** from the diyne alcohol and CO_2. A α-hydroxy ketone **242** is next generated by basic hydrolysis of the carbonate **241** which is followed by the isomeriza-



Scheme 50. Total synthesis of inotilone **5** from acetaldoxime.



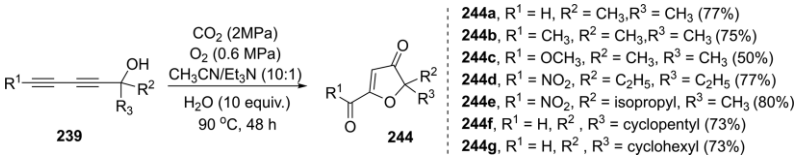
Scheme 51. Carbondioxidemediated synthesis of 2,5-disubstituted-3(2*H*)-furanones from diyne alcohols.

tion of **242** to an allenyl ketone **243**. The 2,5-disubstituted-3(2*H*)-furanone is finally produced by an endo-cyclisation of **243** catalyzed by the base. The authors also demonstrated the possibility for benzylic oxidation of the synthesized 5-benzyl-2,2-disubstituted-3(2*H*)-furanone **240**.[53]

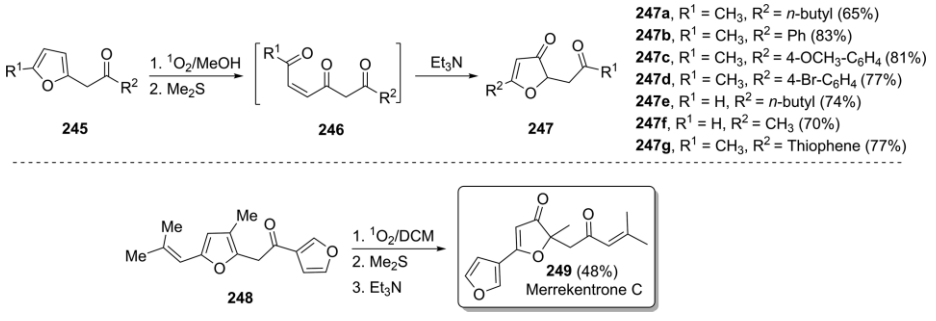
A one-pot process for the synthesis of the substituted-3(2*H*)-furanone **240** and oxidation (with O_2) to 5-benzoyl-2,2-disubstituted-3(*2H*)-furanone **244** was developed and the general applicability was studied in detail (Scheme 52).

Stratakis and co-workers developed a singlet oxygen-mediated photooxygenation of (*β*-keto)-2-substituted furans for the synthesis of substituted 3(*2H*)-furanones (Scheme 53).[54] The first step of the reaction is the oxidation of the substituted furan **245** to the intermediate triketone **246** which then undergoes an intramolecular oxa-Michael reaction to afford a functionalized 3(*2H*)-furanone **247**. The developed methodology was effectively utilized for the total synthesis of merrekentrone C **249**, a furano-sesquiterpene isolated from the roots of the species *Merremia kentrocaulos*.

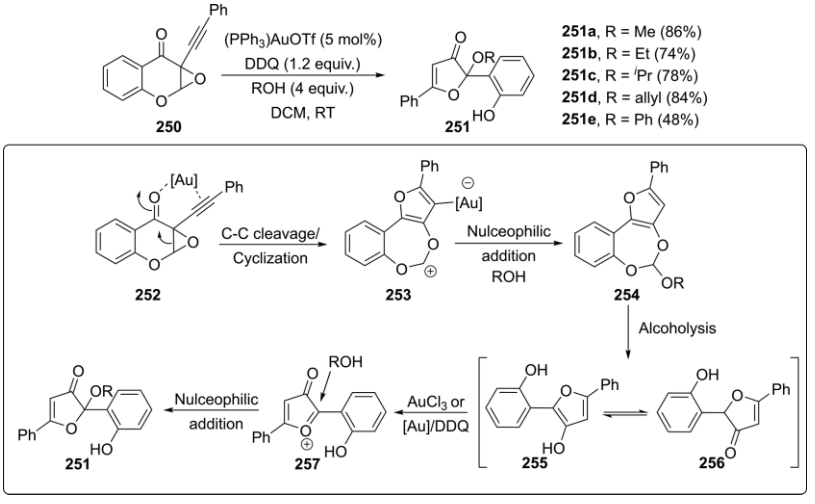
Another gold catalyzed route towards 2,5-disubstituted-3(*2H*)-furanones was illustrated by Hu and co-workers (Scheme 54).[55] The starting 3-alkynyl-oxireno[2,3-b]chromenones **250** were subjected to a Au/DDQ-catalyzed domino process in the presence of a nucleophile (alcohol) in DCM at room temperature. The reaction was found to work satisfactorily for a range of aliphatic and aromatic alcohols affording the corresponding 2,5-disubstituted-3(*2H*)-furanones in moderate to good yields. The mechanism of the domino process involves several stages such as the initial C–C bond cleavage in **252** and cyclization to afford the intermediate **253** which then undergoes nucleophilic addition to the cationic center furnishing the cyclic ortho-ester **254**. Alcoholysis of this intermediate results in the formation of the hydroxyfuran **255** which is in equilibrium with the furanone **256**. The oxonium ion **257** is then gen-



Scheme 52. One-pot synthesis of 5-benzoyl-2,2-dimethyl-3(2*H*)-furanone from diyne alcohols.



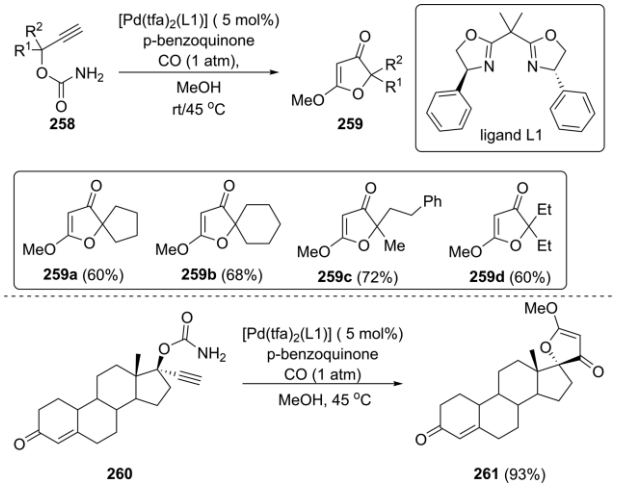
Scheme 53. Formation of a 3(2*H*)-furanone via photooxygenation of ketofuran and total synthesis of merrekentrone C **249**.



Scheme 54. Gold catalyzed domino route towards 2,5-disubstituted-3(2*H*)-furanones.

erated by the oxidation of the C–H bond by stoichiometric Au(II) or catalytic amounts of [Au]/DDQ. The 2,5-disubstituted-3(*2H*)-furanone **251** is finally formed by the nucleophilic addition of the alcohol to the oxonium ion **257**.

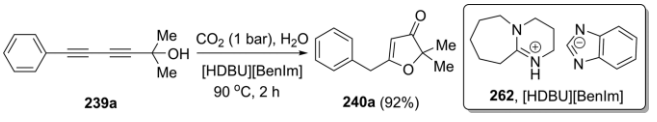
In 2013, Kato and co-workers reported on a Pd-catalyzed strategy for accessing 2,5-disubstituted-3(*2H*)-furanones **259** (Scheme 55).[56] Most of the reactions with propargyl carbamates **258** were carried out in the presence of 5 mol-% of $[Pd(tfa)_2(L1)]$ as catalyst (L1 is a bisoxazoline ligand), 1.5 equiv. of *p*-benzoquinone in methanol as solvent and under 1 atm of carbon monoxide. The reaction proceeded well with acyclic and cyclic substituents and phenyl groups at the propargylic position of the propargyl carbamate. The gem-dialkyl substituents in the propargyl group play a pivotal role in the synthesis of disubstituted-3(*2H*)-furanones, without them the reaction failed.



Scheme 55. Pd-catalyzed synthesis of 2,5-disubstituted-3(*2H*)-furanones from propargyl carbamates.

The authors extended the investigations to the steroidal carbamates **260** and in all cases; the reaction proceeded well affording the respective products in high yields. The mechanism of the reaction follows a 4-step sequence involving a cyclization followed by carbonylation and subsequent decarboxylation and final cyclization.

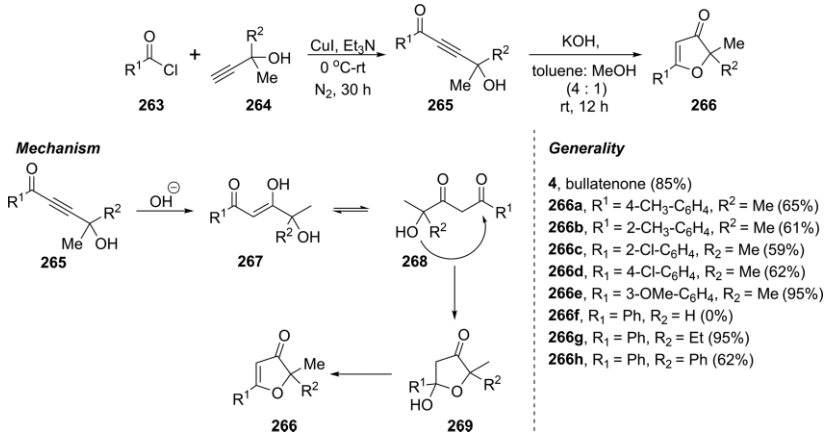
A computer-assisted design for the synthesis of 3(*2H*)-furanones from diyne alcohols **239** was proposed by Wang and co-workers (Scheme 56). The design consisted of catalytic route by a base-functionalized ionic liquid under atmospheric-pressure of CO_2. They developed a moderately basic and highly catalytically active ionic liquid as CO_2 absorbent as well as activator for these processes. It was found that the basicity of the catalyst plays a role in the outcome of these reactions. In this line, weak basicity of the catalyst resulted in a low catalytic activity whereas side reactions were found to occur with strong basic catalysts. Through quantum-chemical calculations, a proper range of basicities was designed. [HDBU][BenIm] **262** was found to be the best catalytic system for the one pot synthesis of 3(*2H*)-furanones from diyne alcohols and moderate basicity was the reason for such high catalytic activity.[57]



Scheme 56. Computer-assisted synthesis of 3(*2H*)-furanones from diyne alcohols.

Intramolecular cyclization of 4-hydroxyalkynones in the presence of KOH to 2,5-disustituted furanones was developed by Panda et al. (Scheme 57).[58] Their method starts with a Cu-catalyzed coupling of an acid chloride and a terminal alkyne, resulting in the formation of 4-hydroxyalkynone **265**. Then the 4-hydroxyalkynone was subjected to base induced intramolecular cyclisation to eventually yielding the disubstituted-3(*2H*)-furanones **266**. The transformation starts with the addition of hydroxyl ion to ynone **265** to provide the enol intermediate **267** which tautomerizes to the 1,3-diketone **268**. The hydroxyl group then adds to the carbonyl carbon forming the furanone **269** from which a molecule of H_2O is finally lost to furnish the disubstituted-3(*2H*)-furanone **266**.

Recently Menche and co-workers reported on the stereochemical assessment of a class of myxobacterial polyketides, tuscolid **270** and tuscorons **271–275** through NMR analysis, molecular modeling and synthetic transformations (Figure 3).[59] Tuscolid is a 22-membered macrolactone ring with an uncom-



Scheme 57. KOH mediated intramolecular cyclization of 4-hydroxyalkynones leading to 2,5-disubstituted-3(*2H*)-furanones **266**.

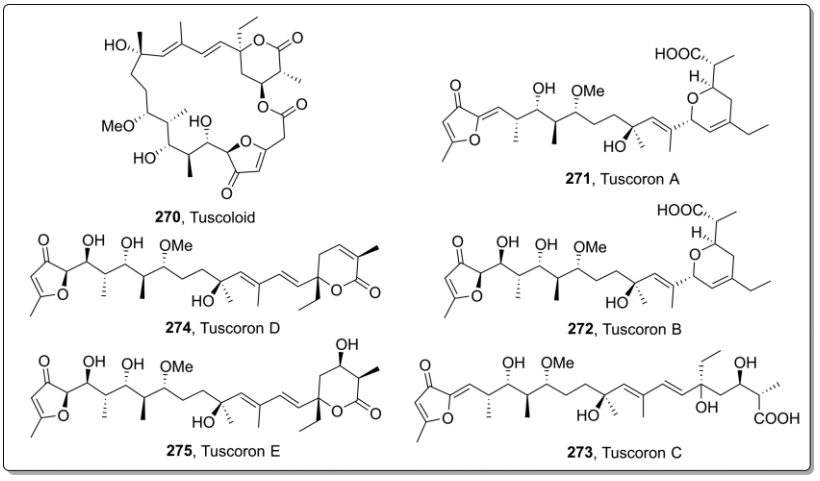
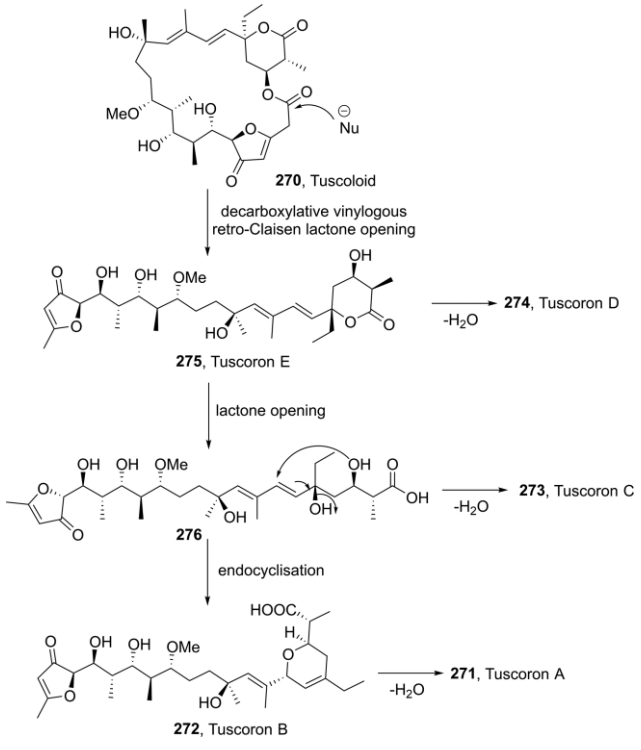


Figure 3. The tuscolid/tuscorons, polyketides isolated from *Sorangium cellulosum*.

mon chiral furanone bearing a bridgehead double bond. The tuscorons are linear compounds constructed of furanone rings and a polypropionate chain. The authors also studied the total synthesis of tuscoron D and E identified from a myxobacterium *Sorangium cellulosum* strain Soce1401. The synthesis involves the construction of three building blocks namely, furanone, polypropionate and lactones.

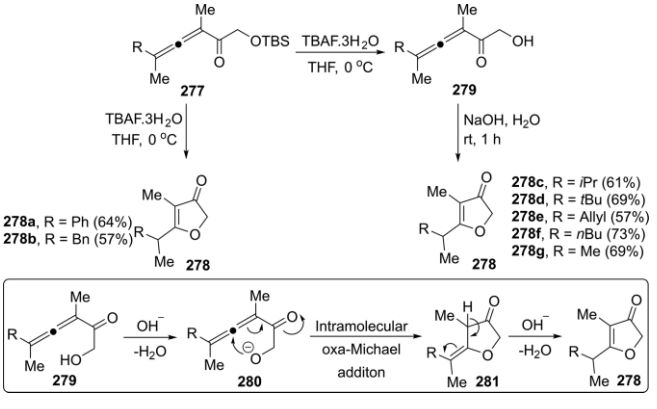
They also studied the tuscolid/tuscorone rearrangement.[59] This transformation commenced with a decarboxylative macrolactone ring-opening of **270** along with a decarboxylation from which tuscoron E **275** is then formed by a vinylogous retro-Claisen condensation. The δ-lactone in **275** is then cleaved to furnish an intermediate **276** which upon an intramolecular S_N2'-type endo-cyclisation provides tuscoron B **272**. The intermediate **276** on elimination of H_2O furnishes tuscoron C **273**. Tuscorons A **271** and D **274** are inturn derived by elimination of H_2O from tuscorons B and E, respectively (Scheme 58).



Scheme 58. Proposed tuscolid/tuscorone rearrangement.

8. Methods for the Synthesis of 4,5-Disubstituted-3(2*H*)-furanones

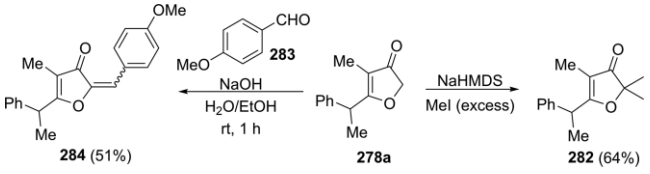
In 2011 Ponooth and Krause revealed a strategy for accessing 4,5-disubstituted-3(2*H*)-furanones by the cycloisomerization of bifunctionalized allenes (Scheme 59).[60] The allene scaffold was cleverly designed by placing the keto and hydroxyl groups in such positions that a base induced cyclisation would result in a substituted 3(2*H*)-furanone moiety. The allenic hydroxy ketone **277** was synthesized from the corresponding propargyl oxirane by a sequential Cu-catalyzed S_N2'-substitution and oxidation process. The phenyl (or benzyl)-substituted allenone (TBS protected) **277** was then treated with TBAF at 0 °C initiating a deprotection-cyclisation cascade affording the 4,5-disubstituted-3(2*H*)-furanone **278** in good yield. Interestingly, the TBS-deprotection of alkyl-substituted allenones afforded hydroxy allenones **279** as the sole products. These alkylated hydroxyl allenones furnished substituted 3(2*H*)-furanones on



Scheme 59. Synthesis of 4,5-disubstituted-3(2*H*)-furanones **278** by the cycloisomerization of allenic hydroxy ketones.

treatment with aqueous NaOH. The proposed mechanism proceeds by an intramolecular oxa-Michael addition (*5-endo-dig*) and subsequent base-catalyzed isomerization of the exocyclic double bond.

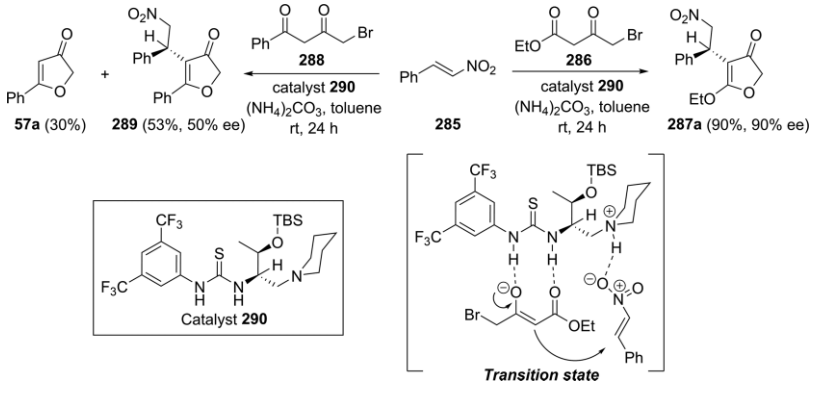
The synthesized 4,5-disubstituted-3(2*H*)-furanones were also subjected to various transformations to introduce additional substituents into the C2-position.[60] Initially the furanone **278a** was treated with an excess of methyl iodide in the presence of NaHMDS as base which afforded the 2,2-dimethyl derivative **282** in 64 % yield. Furthermore, furanone **278a** was subjected to aldol condensation with *p*-methoxybenzaldehyde **283** from which the corresponding adduct **284** was isolated in fair yield (Scheme 60).



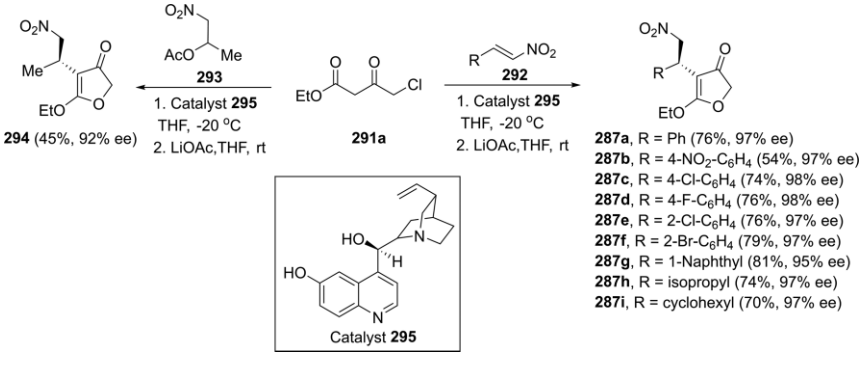
Scheme 60. Synthetic transformations of 4,5-disubstituted-3(2*H*)-furanones.

Lu and co-workers developed a modified Feist–Bénary reaction for the asymmetric synthesis of 4,5-disubstituted-3(2*H*)-furanones.[61] The reaction was performed with ethyl 4-bromoacetoacetate **286** and nitroolefin **285** in the presence of the *L*-threonine-derived tertiary amine/thiourea as a chiral catalyst **290** and $(NH_4)_2CO_3$ as the base. The reaction was found to be general with different aromatic and aliphatic substituted nitroolefins from which the disubstituted-3(2*H*)-furanones were isolated in good yields and high enantioselectivities. The reaction was also tried with 4-bromo-1-phenylbutane-1,3-dione **288** and β-nitrostyrene under the conditions mentioned above. This reaction furnished the expected product **289** in moderate yield and an *ee* of 50 % along with a self-cyclization product **57a** of 4-bromo-1-diketone. The authors proposed a plausible transition state model which features the deprotonation of the β-keto ester to the enolate anion by the tertiary amine group of the catalyst. This moiety engages in hydrogen-bonding interactions with the thiourea unit of the catalyst. In addition, the authors claim that the substrate binding was effected by the ionic interaction between the positively charged ammonium ion with the nitroolefin (Scheme 61).

Soon after, Yan et al. reported another organocatalytic asymmetric approach towards 4,5-disubstituted-3(2*H*)-furanones.[62] In this report, they used 6′-demethyl quinine **295** as the chiral catalyst for effecting the asymmetric Michael addition of 4-haloacetoacetate **291a** to the nitroolefin **292**. An additional base, LiOAc, was used for inducing the intramolecular cyclization in the Michael adduct towards the substituted 3(2*H*)-furanone. The scope of the reaction was investigated by using different aryl and alkyl-substituted nitroolefins. All these reactions afforded the corresponding disubstituted-3(2*H*)-furanones in good yields and excellent enantioselectivities. The authors also tried the reaction of 2-acetyloxy-1-nitro-propane **293** with ethyl 4-chloro-acetoacetate.

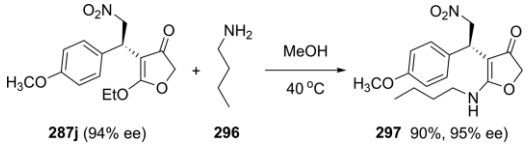


Scheme 61. Asymmetric synthesis of 4,5-disubstituted-3(2*H*)-furanones.



Scheme 62. Asymmetric synthesis of 4,5-disubstituted-3(2*H*)-furanones **287**.

This process was explained to proceed via the in situ formation of (*E*)-1-nitroprop-1-ene (from 2-acetyloxy-1-nitro-propane) onto which 4-chloro-acetoacetate binds to undergo the tandem Michael addition-intramolecular cyclization affording tetronic acid derivative **294** in low yield, but in good enantioselectivity (Scheme 62). The authors synthesized an aza-prostaglandin analogue **297** by treating 3(2*H*)-furanone **287j** with butylamine **296** in MeOH at 40 °C (Scheme 63).[62]



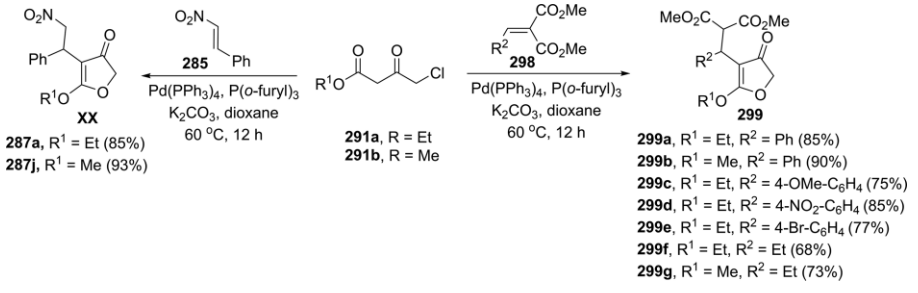
Scheme 63. Synthesis of aza-prostaglandin from 3(2*H*)-furanone **287j**.

In 2013, we came across a serendipitous observation while we were working on a project for the synthesis of substituted cyclopentanones.[63] From the Pd-catalyzed reaction of activated styrene **298** and 4-haloacetoacetate **291** in the presence of a base, we isolated 4,5-disubstituted-3(2*H*)-furanone **299** in contrast to our expectation. Under the optimized condition which consisted of $Pd(PPh_3)_4$ as catalyst, P(*o*-furyl)$_3$ as ligand, K_2CO_3 as base and dioxane as solvent, the reaction was found to be general for a range of aromatic and aliphatic activated alkenes. The reaction was also found to proceed in the absence of any Pd-catalyst, but in lower yields (Scheme 64).

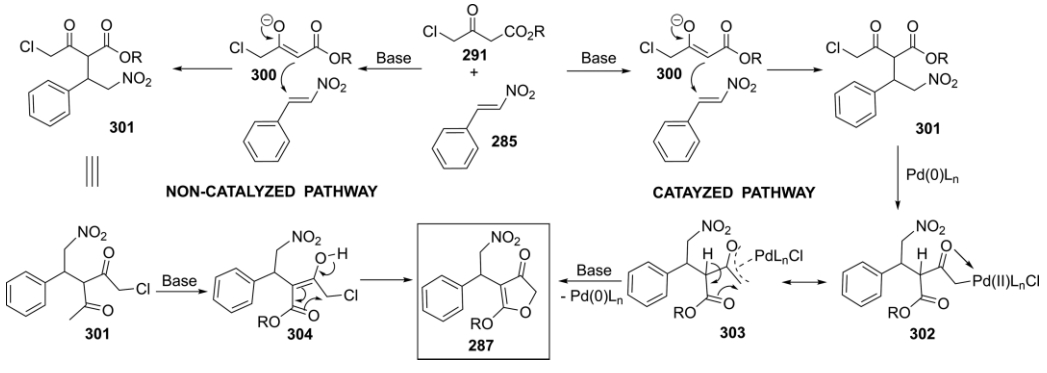
The mechanisms of both the catalyzed and uncatalyzed reactions involve two stages (Scheme 65).[63] The first one being the Michael addition of acetoacetate to the activated styrene. The second stage of the catalyzed process starts with the oxidative addition of Pd(0) to the C–Cl bond resulting in the oxy-π-allyl Pd-intermediate **302**. This is followed by the abstraction of the acidic proton by base and the ester enolate **303** attacks the carbon end of the oxy-π-allyl Pd-intermediate resulting in the formation of the 3(2*H*)-furanone ring. In the uncatalyzed pathway, the ester enolate in the Michael adduct **304** displaces the chlorine substituent forming the furanone moiety.

In 2014, we extended the methodology for introducing different substituents at the C4-position of the 3(2*H*)-furanone ring.[64] This was effected by making use of electrophiles such as activated imines **305** and dialkylazodicarboxylates **307**. The tandem process was found to be general with a variety of tosylimines furnishing the corresponding 4-substituted furanones in good to excellent yields in the presence of a combination of $Pd_2(dba)_3$•$CHCl_3$ as catalyst, dppe as ligand and Na_2CO_3 as base. 4-Hydrazino-3(2*H*)-furanones **308** were obtained in excellent yields by the reaction of 4-haloacetoacetate and dialkylazodicarboxylates in the presence of $Pd(PPh_3)_4$ as catalyst and K_2CO_3 as base (Scheme 66).

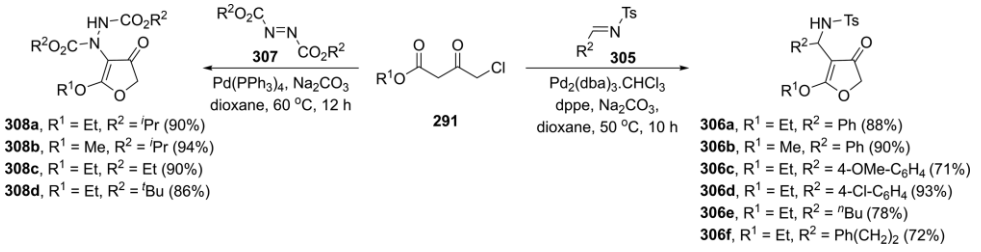
Another report on the utilization of 4-haloacetoactate for the asymmetric synthesis 4,5-disubstituted-3(2*H*)-furanones came from the group of Yu.[65] In the presence of the commercially available quinine catalyst **310** and Na_2CO_3 as base, ethyl 4-bromo-acetoacetate **286** was treated with *N*-substituted maleimide **309** in DCM at 0 °C to afford succinimide substituted 3(2*H*)-furanone **311** (Scheme 67). The reaction was found to be general with a variety of *N*-aryl/alkyl-substituted maleimides and the expected products were isolated in good yields and enantioselectivities. The reaction proceeds via the **TS** where the hydroxyl group of the catalyst activates maleimide by hydrogen bonding and the tertiary amine function of quinine activates the enol form of acetoacetate. This is followed by Michael addi-



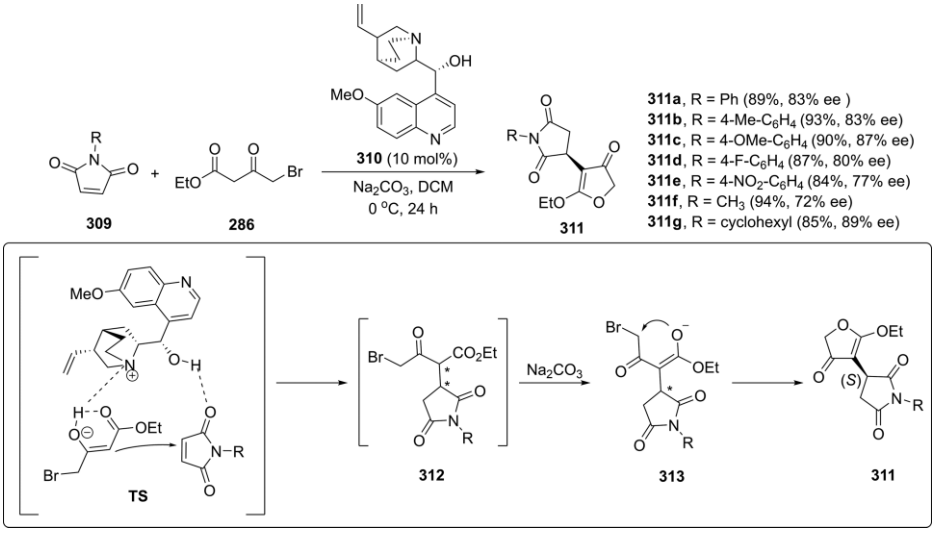
Scheme 64. Pd-catalyzed synthesis of 4,5-disubstituted-3(2*H*)-furanones **299** and **287**.



Scheme 65. Mechanism of Pd-catalyzed and uncatalyzed synthesis of 4,5-disubstituted-3(2*H*)-furanones.



Scheme 66. Pd-catalyzed synthesis of 4,5-disubstituted-3(2*H*)-furanones.

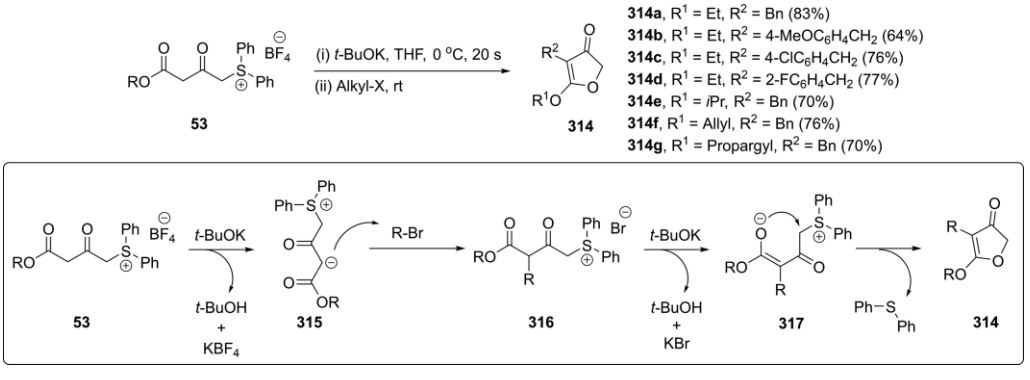


Scheme 67. Synthesis of succinimide substituted 3(2*H*)-furanones **311**.

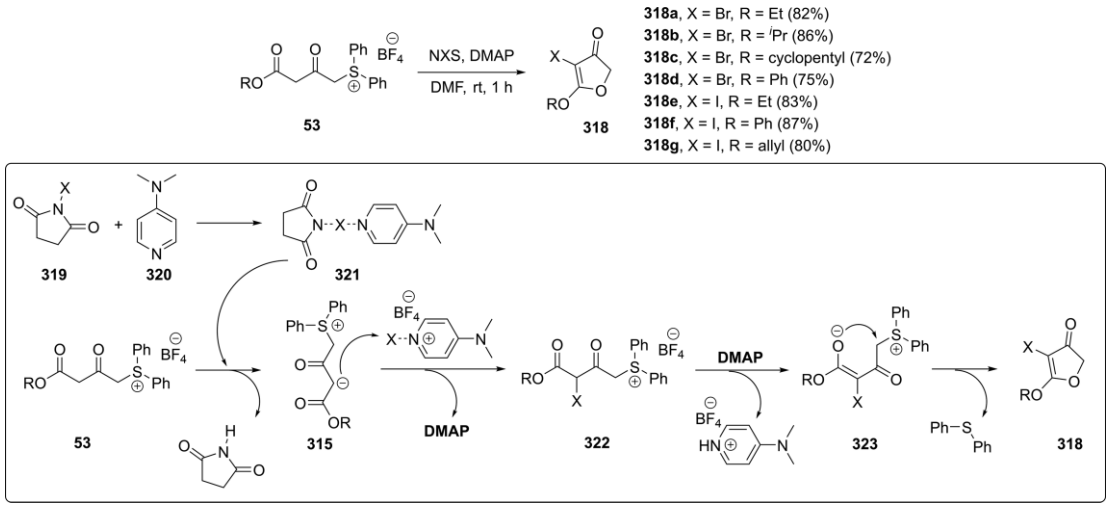
tion of the enolate to the maleimide from the *re*-face. The Michael adduct **312** then undergoes a base induced intramolecular *O*-alkylation to generate the disubstituted-3(2*H*)-furanone **311** with (*S*)-configuration.

Kawano and co-workers reported an interesting method for the synthesis of 4-alkyl-5-alkoxy-3(2*H*)-furanones by an alkylative intramolecular cyclization protocol (Scheme 68). In this approach, the authors utilized diphenylsulfonium tetrafluoroborate as the leaving group on the acetoacetate moiety rather than a halogen substituent as in earlier reports. When 4-diphenylsulfonium acetoacetate **53** was treated with benzyl bromide and a base in THF, the corresponding 4-benzyl-substituted 3(2*H*)-furanone **314a** was formed. The reaction was found to be general with a range of substituted benzyl and alkyl bromides. The reaction proceeds via the formation of an enolate **315** by the reaction of 4-diphenylsulfonium acetoacetate **53** with the base. This enolate then reacts with the alkyl halide to form the alkylated intermediate **316**. This is followed by the abstraction of the second acidic proton and the resultant enolate **317** undergoes an intramolecular cyclization and eliminates diphenyl sulfide leading to the formation of 4-alkyl-5-alkoxy-3(2*H*)-furanones **314**.[66]

A short time later the same authors reported a similar approach towards 4-halo-5-alkoxy-3(2*H*)-furanones (Scheme 69). This halogenative intramolecular cyclization strategy was also effected by using diphenylsulfonium tetrafluoroborate as the

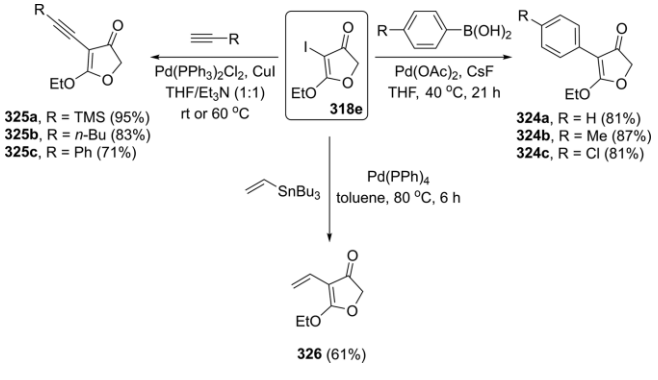


Scheme 68. Synthesis of 4-alkyl-5-alkoxy-3(2*H*)-furanones **314**.



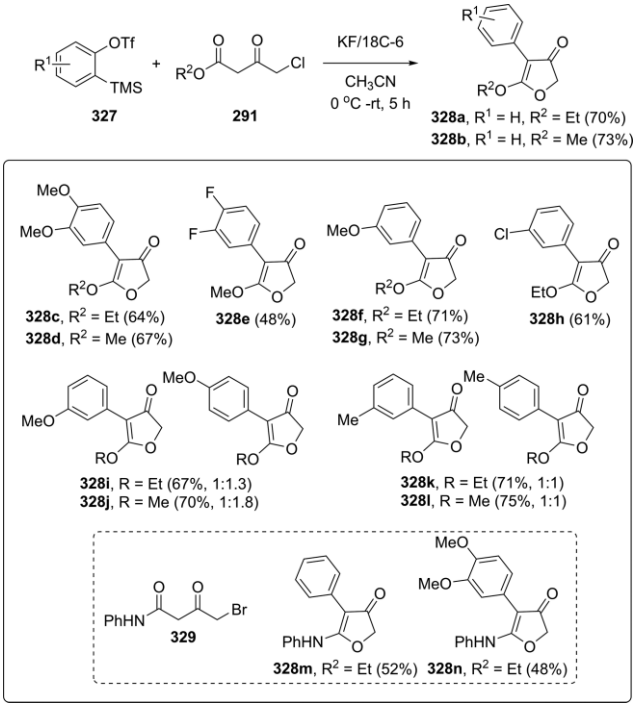
Scheme 69. Synthesis of 4-halo-5-alkoxy-3(2*H*)-furanones **318**.

leaving group. In this case, 4-diphenylsulfonium acetoacetate **53** was treated with *N*-halosuccinimide and DMAP in DMF at room temperature. and the corresponding 4-halo-substituted 3(2*H*)-furanone **318** was formed. Irrespective of the alkyl or aryl substituent on the ester group of the acetoacetate, the reaction worked well with NIS and NBS affording the respective products in good yields. The initial step of the reaction consists in the formation of the intermediate **321** by the reaction of NXS and DMAP. This intermediate then abstracts the acidic proton in **53** and eliminates succinimide. The anion **315** generated subsequently takes up the halogen atom from the pyridinium salt resulting in the formation of 3-halogenated sulfonium salt **322** and DMAP. Subsequently an ester enolate **323** is generated by the regenerated DMAP which undergoes an intramolecular cyclization furnishing the 4-halo-5-alkoxy-3(2*H*)-furanone after the elimination of diphenyl sulfide.[67] The synthesized 4-iodo-5-ethoxy-3(2*H*)-furanone **318e** was then subjected to different Pd-catalyzed coupling reactions such as Suzuki, Sonogashira, and Stille coupling to introduce different substituents at the 4-postion of the 3(2*H*)-furanone moiety (Scheme 70).[67]

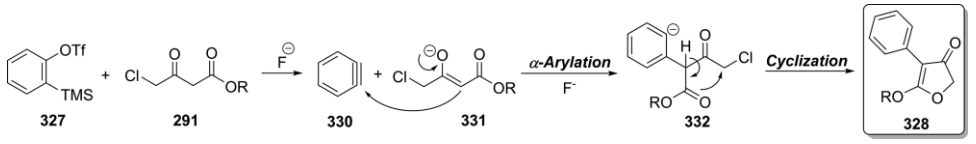


Scheme 70. Synthetic transformations of 4-halo-5-alkoxy-3(2*H*)-furanones **318**.

Very recently, we reported a methodology for the synthesis of 4-aryl-3(2*H*)-furanone **328** by the reaction of 4-haloacetoacetate **291** with an aryne (Scheme 71). The reaction was carried out with a combination of KF (as aryne generator and base) and 18-crown-6 in CH_3CN. The reaction was found to work well with a range of arynes furnishing the respective 4-aryl-3(2*H*)-furanones in moderate to good yields. This tandem process was found to proceed satisfactorily with disubstituted aryne precursors such as 4,5-dimethoxy-*o*-silylphenyl triflate and 4,5-difluoro-*o*-silylphenyl triflate. Single regioisomers were isolated from the reaction mixtures involving 3-methoxy-1,2-benzyne and 3-chloro-1,2-benzyne. Whereas inseparable mixtures of regioisomers were formed in the reaction of 4-haloacetoacetates with different 4-substituted 1,2-benzynes. We could also change the substituent at the 5-position from alkoxy to amino group by starting with 4-bromo-3-oxo-*N*-phenylbutanamide **329**. Furanones **328m** and **328n** were obtained in moderate



Scheme 71. Synthesis of 4-aryl-3(2*H*)-furanones.



Scheme 72. Mechanism for the formation of 4-aryl-3(2*H*)-furanones.

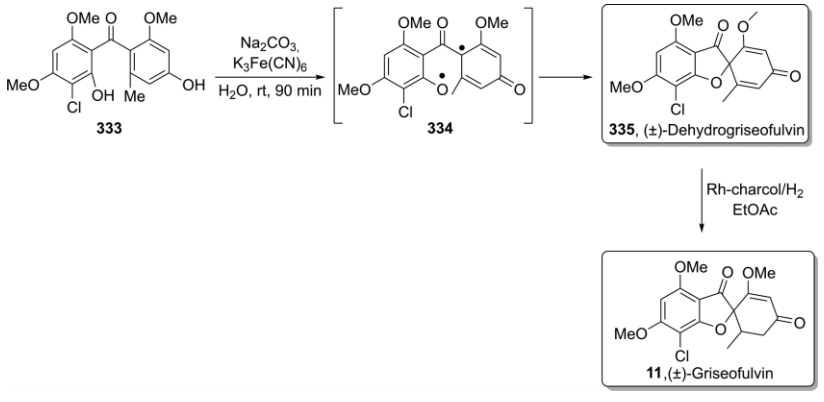
yields by the reaction of **329** with unsubstituted benzyne and dimethoxybenzyne.[68] A plausible mechanism for the formation of these 4-aryl-3-(2*H*)-furanones was proposed and is based on experimental results and literature reports.[68] The reaction commences with the fluoride ion induced formation of aryne **330** and enolate **331**.

The intermediate then participates in a nucleophilic addition to the aryne generating the -arylated anionic species **332**. The anionic center in **332** is next quenched by the proton at the activated carbon atom which, inturn, generates the ester enolate that undergoes intramolecular ring closure furnishing the 4-aryl-3-(2*H*)-furanone **328** (Scheme 72).

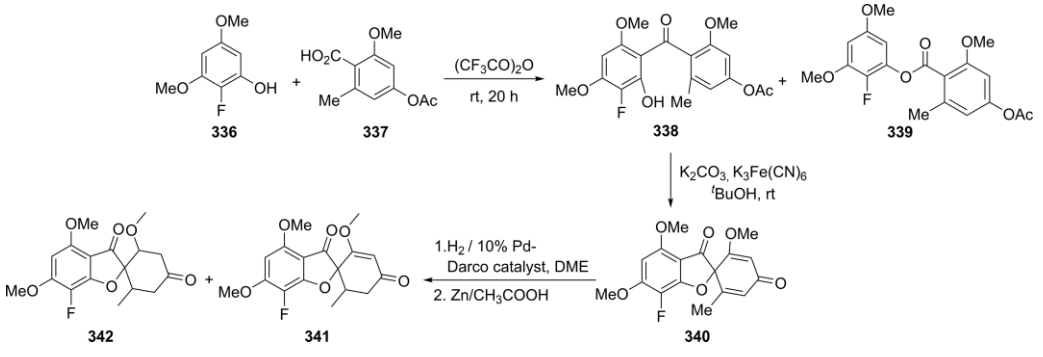
9. Methods for the Synthesis of 2,4,5-Trisubstituted-3(2*H*)-furanones

In 1961 an oxidative coupling of phenolic radicals has been reported by Day et al. for the synthesis of griseofulvin **11**, a benzo-3(2*H*)-furanone from 3-chloro-2,4′-dihydroxy-2′,4,6-trimethoxy-6′-methylbenzophenone **333** (Scheme 73). This molecule was first isolated from *penicillium griseofulvum* and it is considered a classical antifungal agent. The first step in the total synthesis was the C–O coupling of the diradical **334** derived from **333** to dehydrogriseofulvin **335** followed by reduction to (±)-griseofulvin **11**. Reduction of **335** with rhodium-on-charcoal, pre-reduced in the presence of selenium dioxide, gave higher yields than rhodium-on-charcoal alone.[69]

Wendler et al. in 1963 synthesized griseofulvin and its derivatives as potential antifungal agents (Scheme 74). The synthesis of the fluoro-derivative of griseofulvin **341** was initiated by the coupling of 2-fluoro-3,5-dimethoxyphenol **336** and 2-methoxy-4-acetoxy-6-methylbenzoic acid **337** in the presence of trifluoroacetic anhydride at 20–25 °C. This coupling was found to be temperature dependent as at lower temperature *O*-acylation product **339** was predominantly formed rather than the required benzophenone **338**. Oxidation of **338** with potassium gave the intermediate **340** which upon hydrogenation over 10 % Pd/C followed by conversion of the dienone by treatment with zinc in acetic acid afforded the (±)-7-fluoro-7-dechlorogriseofulvin **341**. A minor amount of the dihydroderivative **342**



Scheme 73. Total synthesis of (±)-griseofulvin **11**.



Scheme 74. Total synthesis of (±)-7-fluoro-7-dechlorogriseofulvin **341**.

was also formed. (±)-griseofulvin **11** was also synthesized using the same procedure by starting from 2-chloro-3,5-dimethoxyphenol.[70]

The authors also provided another strategy for the synthesis of (+)-7-fluoro-7-dechloro-griseofulvin **341** from norgriseofulvic acid.[70] First **343** was converted into the 4′-isopropyl ether intermediate **344** which was converted to a mixture of dienones **345** and **346**. This mixture of dienones was reduced to a mixture of the phenols which was methylated with diazomethane. Finally, deprotection and methylation provided the (+)-7-fluoro-7-dechlorogriseofulvin **341** and (+)-griseofulvin **11** (Scheme 75).

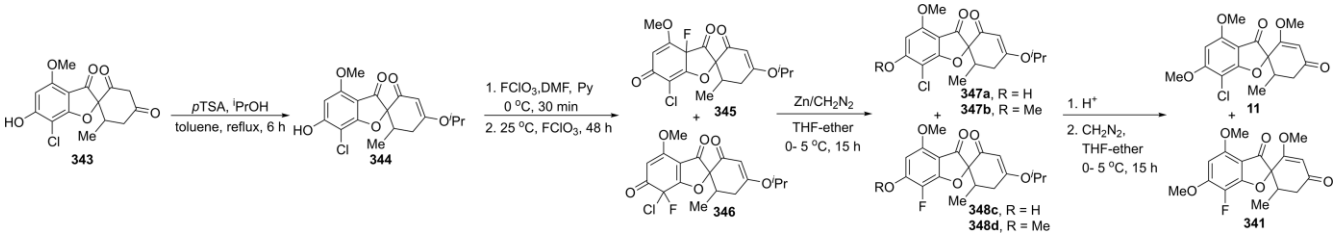
The authors also demonstrated the synthesis of (–)-griseofulvin and (+)-griseofulvin, for which (±)-griseofulvin was hydrolysed to (±)-griseofulvic acid by heating with a mixture of acetic and sulfuric acid. Then (±)-griseofulvic acid was treated with cinchonine methohydroxide to generate diastereomeric salts, from which the salt of (+)-griseofulvic acid was separated by resolution. This salt was converted to (+)-griseofulvicacid and further methylation with diazomethane afforded (+)-isogriseofulvin and (+)-griseofulvin.[70]

In 1964, Stork and Tomasz reported the synthesis of *dL*-griseofulvin from 2-chloro-3,5-dimethoxyphenol **349**.[71] An intramolecular nucleophilic substitution in **350** furnished the coumaranone **351**. Its reaction with methoxyethynyl propenyl ketone **352** gave the *dl*-griseofulvin via double Michael addition of the active methylene moiety of **351** to vinyl ethynyl ketone **352**. This synthesis was free from its epimer *dL*-epigriseofulvin due to its lesser stability and because the reaction was kinetically controlled. The observed stereospecificity was attributed to the better overlap observed in the transition state **354** between the electron-rich enolate ion and the unsaturated ketone (Scheme 76).

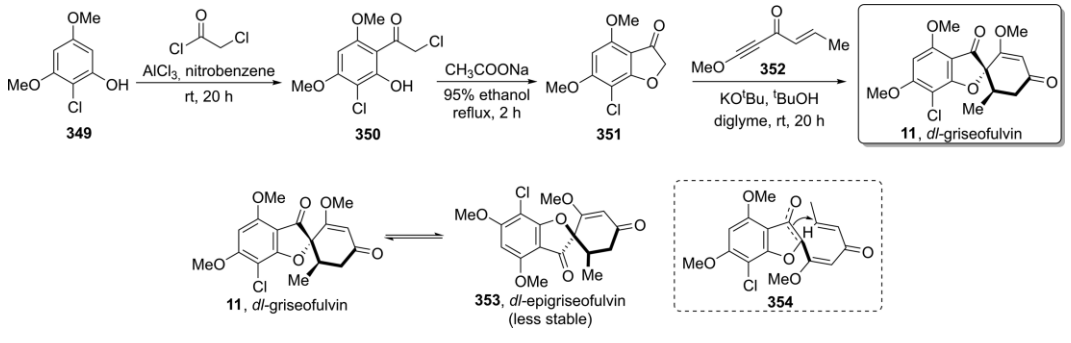
In 1966, Henry and Silverstein reported the synthesis of a flavor component of pineapple, namely 4-hydroxy-2,5-dimethyl-3(2*H*)-furanone **362** starting with a base-catalyzed condensation of dimethyl oxalate **355** and dimethyl diglycolate **356** (Scheme 77). The diol **357** obtained from the condensation was then benzylated and the resulting product **358** was reduced with $LiAlH_4$. The resulting diol **359** was next subjected to benzoylation to afford the compound **360** which on catalytic hydrogenation provided the dimethyl dihydroxylfuran **361** that readily tautomerizes to the natural product 4-hydroxy-2,5-dimethyl-3(2*H*)-furanone **362**. An additional, longer route towards **362** was also developed starting from intermediate **360** which was converted into the thioether **363** which on desulfurization with Raney-Ni and a subsequent reduction with Pd/C afforded the dihydroxylfuran **361**.[72]

Later, Danishefsky and Walker presented a stereospecific synthesis of griseofulvin from the *o*-chloroacetylphenol derivative **350** and 1,1-dimethoxy-3-trimethylsilyloxy-1,3-butadiene **370** (Scheme 78). The first step of the total synthesis was the conversion of the phenol derivative **350** to its acetate **365**. This transformation was followed by a NaH-mediated diketone synthesis in which the generated oxyanion in **366** displaces the halogen substituent affording a mixture of *E*-and *Z*-isomers of enolized 3(*2H*)-benzofuranone **367**. Further, **367** was converted into a sulfide **368** and then a sulfoxide **369**. A Diels-Alder cycloaddition of this sulfoxide with diene **370** gave the *dl*-dehydrogriseofulvin **335** which upon selective hydrogenation furnished *dL*-griseofulvin **11**.[73]

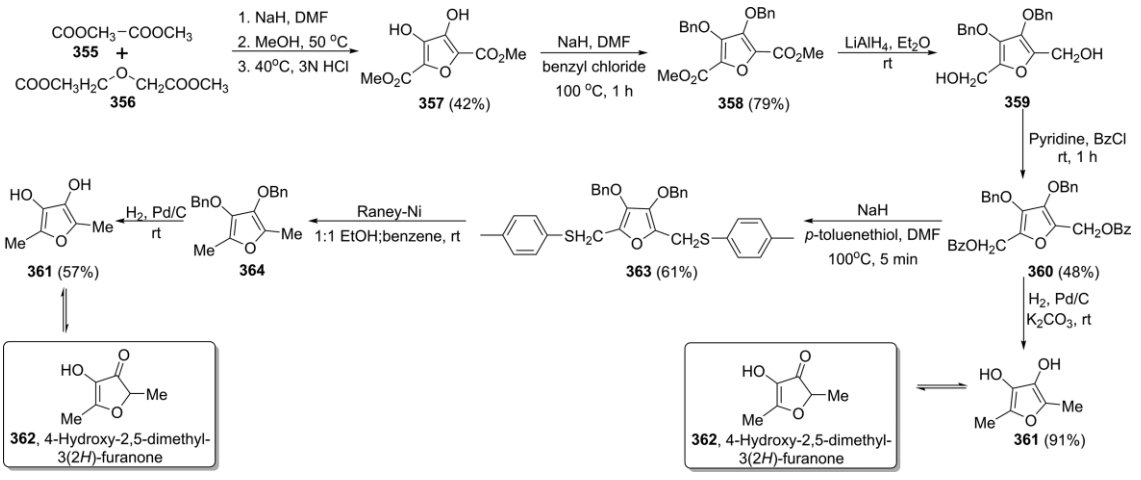
Another total synthesis of (+)-griseofulvin was reported by Pirrung and co-workers in 1991 (Scheme 79). Their approach was initiated by the chlorination of dimethoxyphenol and followed by acetylation to provide **372**. Fries rearrangement of **372**, followed by Mitsunobu reaction generated a chiral centre in **373**. The *S*-ether **373** was then methoxycarbonylated and the resulting β-keto ester was converted into the key diazo ketone intermediate **374** via a diazo group transfer. Its decomposition



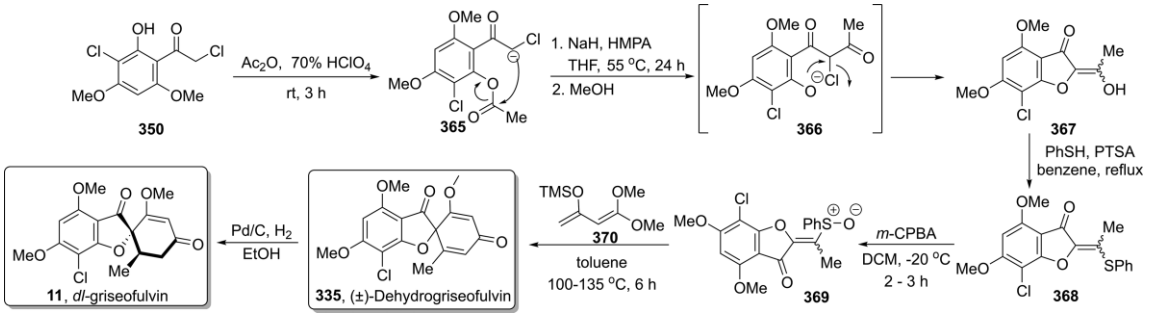
Scheme 75. Total synthesis of (+)-7-fluoro-7-dechlorogriseofulvin **341** and (+)-griseofulvin **11**.



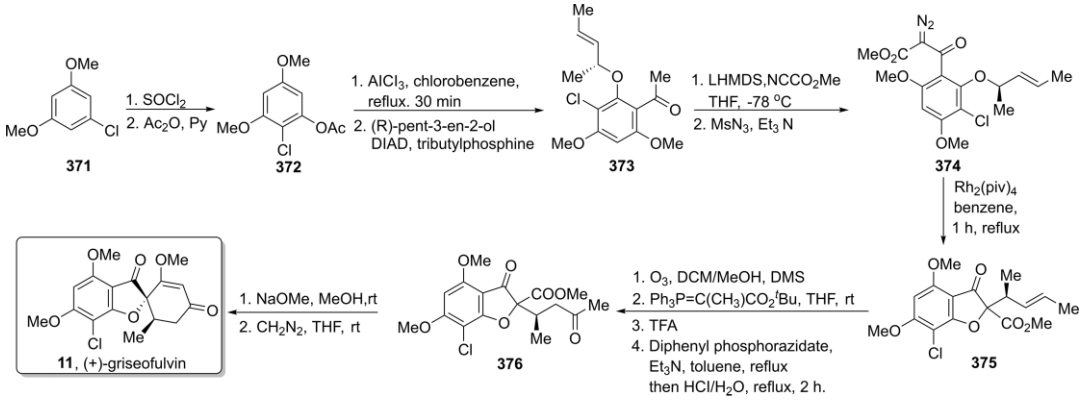
Scheme 76. Total synthesis of *dl*-griseofulvin **11**.



Scheme 77. Synthesis of 4-hydroxy-2,5-dimethyl-3(2*H*)-furanone **362**.



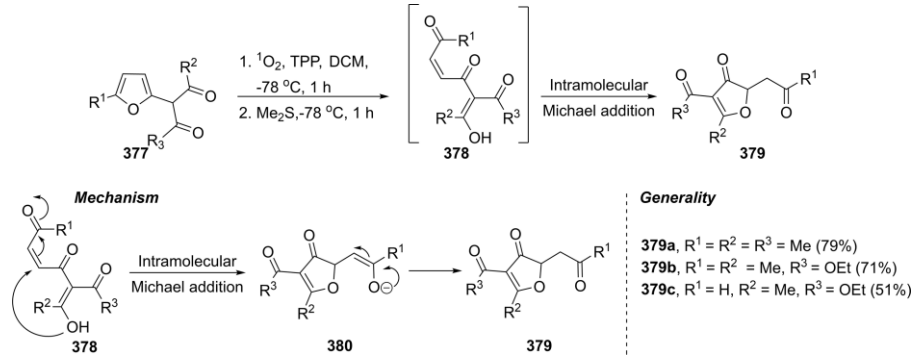
Scheme 78. Total synthesis of *dl*-griseofulvin **11**.



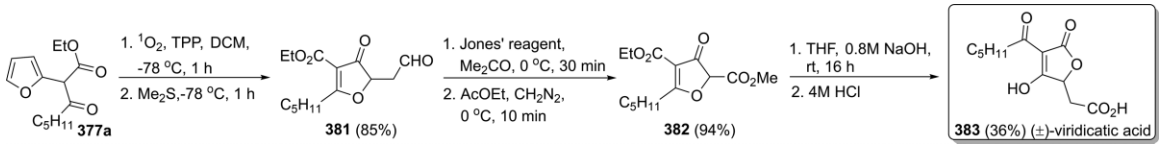
Scheme 79. Total synthesis of (+)-griseofulvin **11**.

in the presence of 5 mol-% of a $Rh_2(piv)_4$ catalyst in refluxing benzene for 1 h provided the sigmatropically rearranged product **375**. Subjecting **375** to a 4-step synthetic transformation gave the methyl ketone **376** which upon Dieckmann cyclization yielded griseofulvic acid and then (+)-griseofulvin **11**.[74]

In 1988, a singlet oxygen mediated synthesis of functionalized 3(2*H*)-furanones was reported by Scettri and co-workers from 2-(2-furyl)-1,3-dicarbonyl compounds (Scheme 80).[75] The sequence was effected by photoirradiation (with a 300 W lamp) of 2-(2-furyl)-1,3-dicarbonyl compounds **377** in the presence of tetraphenylporphyrin at –78 °C for 1 h. The irradiation was monitored by treatment with Me_2S from which 2,4,5-trisubstituted-3(2*H*)-furanones **379** were isolated. The reaction proceeds via a photooxidation of the furan nucleus followed by reduction with Me_2S, to a cross-conjugated, open chain intermediate **378**. The intramolecular Michael addition of enolic OH to the activated C=C bond of the enetrione **378** furnishes the final product. These authors effectively utilized the developed methodology for the synthesis of a naturally occurring metabolite of *Penicilliumviridicaticum*, (±)-viridicatic acid **383** (Scheme 81). The crucial



Scheme 80. Singlet oxygen mediated synthesis of 2,4,5-trisubstituted-3(2*H*)-furanones from 2-(2-furyl)-1 3-dicarbonyl compounds.



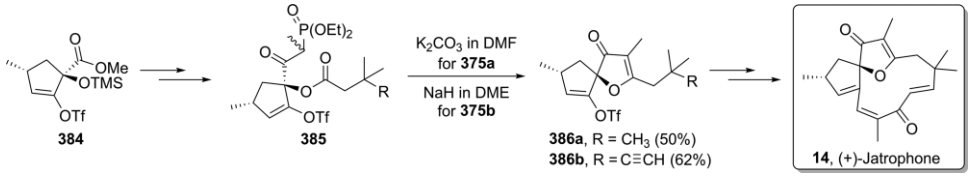
Scheme 81. Synthesis of (±)-viridicatic acids **383**.

intermediate **381**, a 2,4,5-trisubstituted-3(2*H*)-furanone, was synthesized in 80 % yield starting from the 1,3-dicarbonyl-substituted furan **377a**.[75]

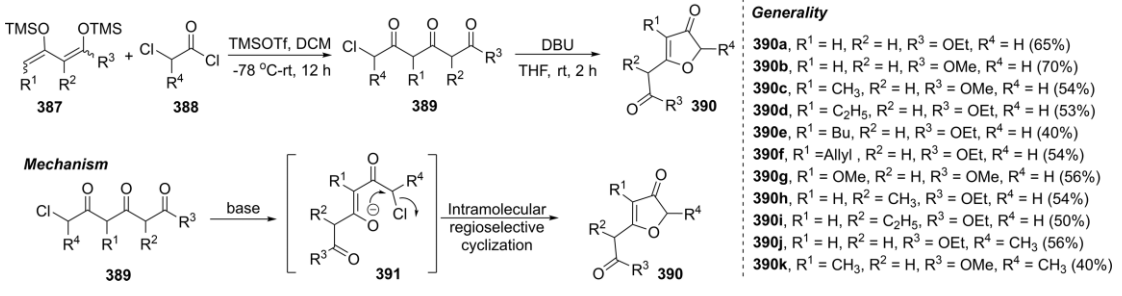
The first total synthesis of (+)-jatrophone **14** in its natural enantiomeric form was reported by Han and Wiemer in 1992.[76] The synthesis of the 3(2H)-furanone core containing natural product was completed in 12 steps from (R)-(+)-3-methyladipic acid in an overall yield of 15 %. The spirocyclic 3(2*H*)-furanone intermediate **386** was prepared by an intramolecular Horner-Wadsworth-Emmons condensation of a phosphonate building block **385** (Scheme 82).

A chemo and regioselective pathway for the synthesis of 2,4,5-trisubstituted-3(2*H*)-furanone was reported in 2000 by Langer and Krummel (Scheme 83). These authors found that when synthons of 1,3-dicarbonyl compounds were treated with chloroacetyl chloride **388** under Lewis acid catalysis conditions, 6-chloro-3,5-dioxo esters **389** were formed which could be easily converted to trisubstituted-3(2*H*)-furanones **390** by treatment with a base. In this study, they used different 1,3-bis(trimethylsiloxy)buta-1,3-dienes **387** with a range of alkyl, benzyl and allyl substituents and all transformations afforded the respective furanones in high yields and selectivities. The 6-chloro-3,5-dioxo ester **389** upon treatment with a base generates the enolate **391** which undergoes regioselective cyclization to furnish trisubstituted-3(2*H*)-furanones.[77]

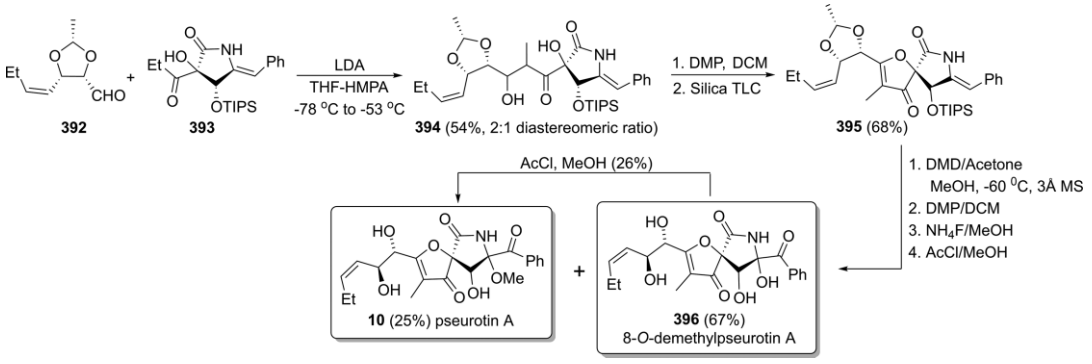
Hayashiet al. in 2003 reported an asymmetric total synthesis of pseurotin A **10**. It is a secondary microbial metabolite isolated from a culture broth of *Pseudeurotiumovalis* (strain S2269/F). The authors also demonstrated the total synthesis of 8-*O*-demethylpseurotin A **396**, another natural product isolated from submerged cultures of an osmophilic *Aspergillus fumigatus* strain. Both metabolites possess chitin synthase inhibitory activ-



Scheme 82. Synthesis of a spiro-3(2*H*)-furanone intermediate in the total synthesis of (+)-jatrophone **14**.



Scheme 83. Chemo- and regioselective synthesis of functionalized 3(2*H*)-furanones from 1,3-bis(trimethylsiloxy)buta-1,3-dienes.



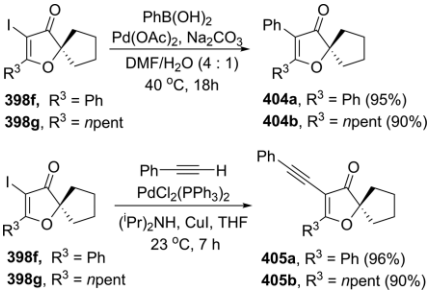
Scheme 84. Total synthesis of pseurotin A **10** and 8-*O*-demethylpseurotin A **396**.

ity and pseurotin A was found to induce cell differentiation of PC12 cells.[78]

These molecules have a highly substituted and oxygenated skeleton with five chiral centers in the core structure. The aldol product **394** was synthesized in 54 % yield (2:1 diastereomeric ratio) by the reaction of the lithium enolate of **393** with the aldehyde **392**. The spirocyclic-3(2*H*)-furanone **395** was obtained from the aldol **394** by a two-step process involving an oxidation of the alcohol function followed by silica mediated intramolecular cyclization. Multiple transformations starting from the intermediate **395** subsequently furnished the final natural products pseurotin A and 8-*O*-demethylpseurotin A (Scheme 84).[79]

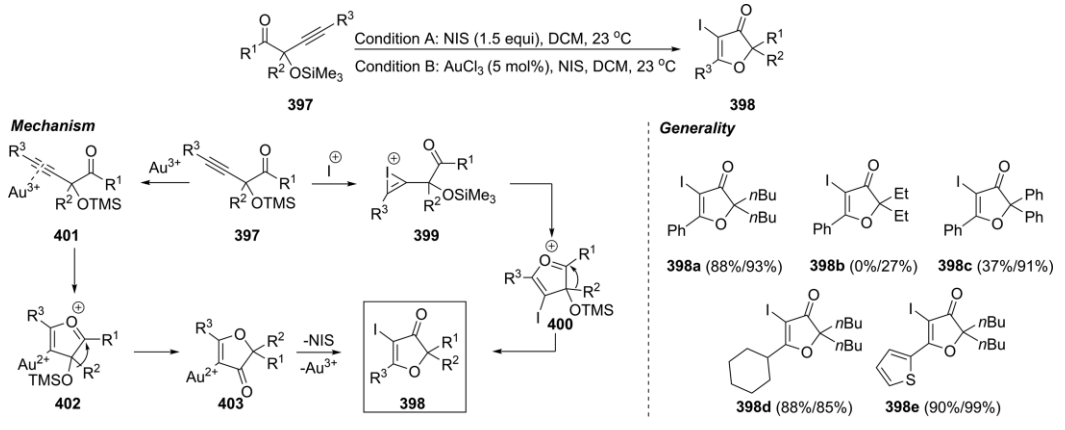
In 2007, Crone and Kirsch reported two reactions utilizing 2-alkynyl-2-silyloxy carbonyl compounds for the synthesis of 4-iodo-3(2*H*)-furanones (Scheme 85). The first reaction follows an electrophilic cyclization pathway induced by *N*-iodosuccinimide while the second proceeds as a gold catalyzed tandem reaction followed by 1,2-migration. In both cases the corresponding 4-iodo-3(2*H*)-furanone **398** was formed as the product, while a significant increase in reaction rate with lower reaction time was observed when a Au(III) catalyst was employed. When the substituents R^3 on the alkyne were changed from aryl, alkenyl, and alkyl groups to acyclic substrates, the yield was found to be meager. The low rate of phenyl migration also contributed to the poor yield of **398c**. The NIS mediated reaction is triggered by an electrophilic attack of iodonium ion on the triple bond in **397** followed by the nucleophilic attack of the carbonyl oxygen to generate **401**. The oxonium ion **400** then undergoes a 1,2-migration giving rise to 4-iodo-3-furanone **398** through a formal α-ketol rearrangement. The gold catalyzed mechanism involves the coordination of Au^{3+} to the alkynyl functionality followed by 1,2-migration to afford intermediate **403**. Finally, NIS induces a iododemetalation in **403** leading to the formation of 4-iodo-3(2*H*)-furanone **398**.[80]

Once in hand, the authors transformed the 4-iodo-3(2*H*)-furanones **398f** and **398g** into fully substituted 3(2*H*)-furanones by Suzuki and Sonogashira coupling processes as shown in Scheme 86.[80]

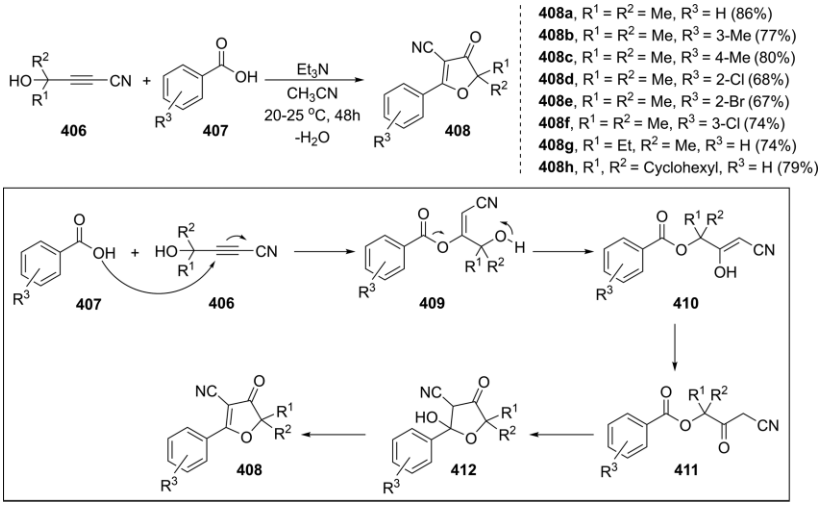


Scheme 86. Synthesis of 2,4,5-trisubstituted-3(2*H*)-furanones **404** and **405**.

In 2010 Trofimov and co-workers described the synthesis of 4-cyano-3(2*H*)-furanones **408** from α,β-acetylenic γ-hydroxy nitriles **406** and arenecarboxylic acids **407** under metal free



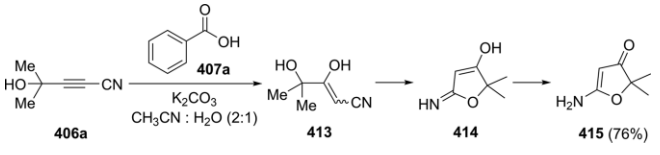
Scheme 85. NIS mediated/Au-catalyzed synthesis of 2,4,5-trisubstituted-3(2*H*)-furanones **398**.



Scheme 87. Synthesis of 2,4,5-trisubstituted-3(2*H*)-furanones **408** from α, β-acetylenic-γ-hydroxy nitriles **406**.

conditions (Scheme 87). The reaction was found to be general with a range of substituted acetylenes **406** and arenecarboxylic acids **407**.

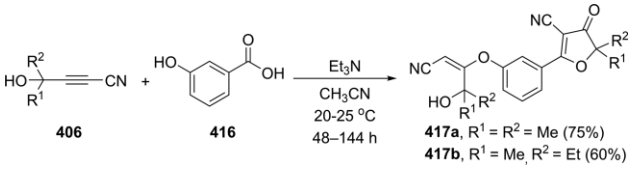
The reaction follows a tandem mode which is initiated by the formation of the enol ester **409** by a nucleophilic addition of arenecarboxylic acids across the triple bonds of alkynes. An intramolecular transesterification occurs in **409** to afford the enol **410** which subsequently tautomerizes to the keto ester **411**. Hemiacetal **412** is formed by a ring closure of **411** by intramolecular Claisen condensation. Ultimately dehydration of **412** furnishes the expected 4-cyano-3(2*H*)-furanone. This reaction pathway is supported by isolating the intermediate keto ester **411** using 10 mol-% of K_2CO_3 as base in the reaction instead of Et_3N. When the intermediate **411** was allowed to react under the optimized conditions, the expected 3(2*H*)-furanone was formed as the sole product.[81] The authors have synthesized 5-amino-2,2-dimethyl-3(2*H*)-furanone **415** from the same acetylene **406a** and arenecarboxylic acid using K_2CO_3 as the base and a 2:1-mixture of CH_3CN and water as solvent (Scheme 88).[81]



Scheme 88. Synthesis of 2,5-disubstituted-3(2*H*)-furanone **415** from α, β-acetylenic-γ-hydroxy nitriles **406a**.

In 2014 the same group revealed the reaction of α,β-acetylenic γ-hydroxy nitriles **406** with 3-hydroxybenzoic acid **416** (Scheme 89). It resulted in the formation of more highly functionalized 4-cyano-3(2*H*)-furanones **417**, namely 4-oxo-2-{3-[(1*Z*)-(cyanoalk-1-en-2-yl)oxy]phenyl}-4,5-dihydrofuran-3-carbonitriles under the same reaction conditions.[82]

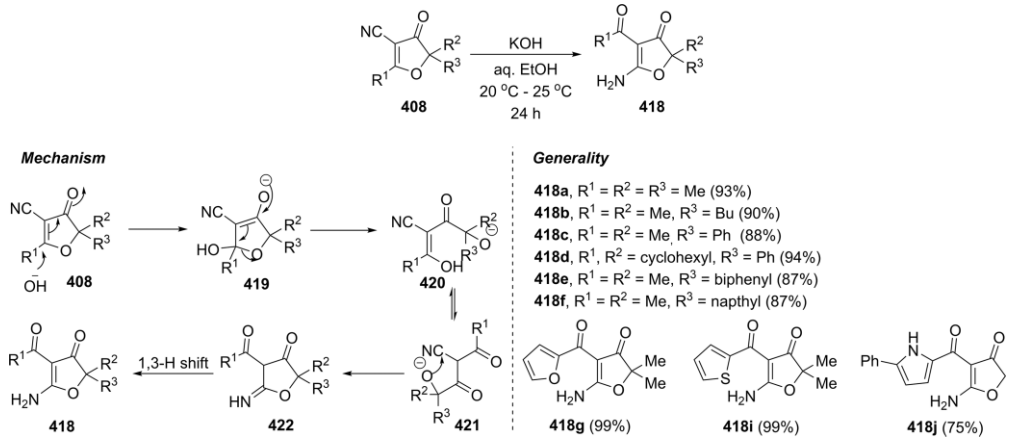
Shemyakina and co-workers effectively utilized the previously reported 4-cyano-3(2*H*)-furanones for the synthesis of 5-amino-3(2*H*)-furanones by a base catalyzed ring-cleavage and



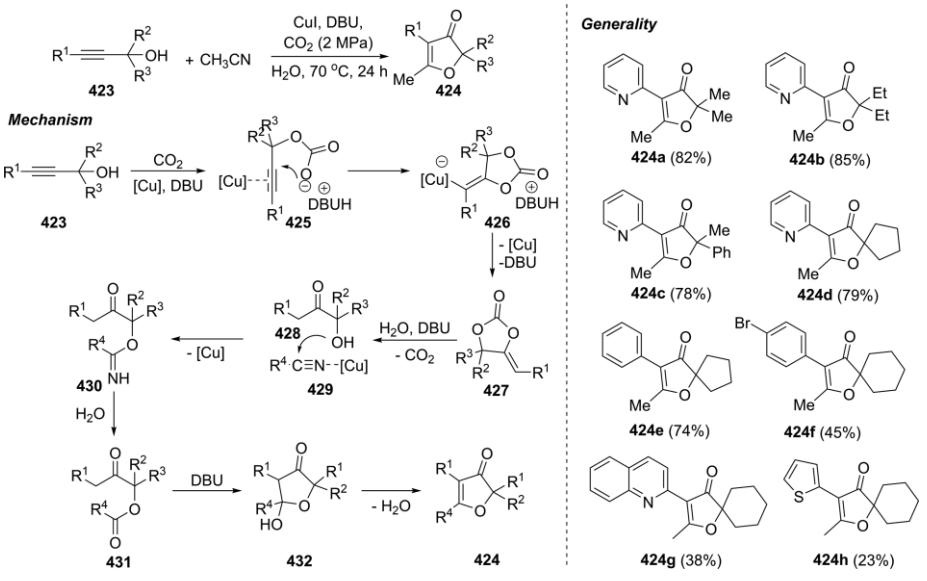
Scheme 89. Synthesis of 2,4,5-trisubstituted-3(2*H*)-furanones **406** from α, β-acetylenic-γ-hydroxy nitriles **395**.

recyclization pathway (Scheme 90). The reaction was monitored by IR spectroscopy specifically by following the disappearance of the C=C–C≡N bands at 2230–2211cm^{-1}. The structure of the 4-cyano-3(2*H*)-furanones **408** was found to influence the reaction rate. For alkyl-substituted derivatives the process was completed within 5 minutes, while in the case of phenyl, biphenyl or naphthyl groups 20–40 minutes were required. 5-Furanyl and 5-thienyl substituents reduced the reaction rate and full conversion was achieved after 3 hours only. This observation can be explained by the electron-donating ability of the substituents at 5-position that complicates the nucleophilic addition of water. Electronic and steric effects of aryl and heteroaryl rings also contribute to this observation.[83]

Another CO_2 mediated and Cu-catalyzed one-pot reaction for the synthesis of highly substituted 3(2*H*)-furanones from nitriles and propargylic alcohols was reported in 2011 (Scheme 91). In this transformation, one of the two oxygen atoms of carbon dioxide is incorporated into the 3(2*H*)-furanone moiety. The nitrile acts as both the reactant and solvent. Moreover, copper salts also have dual roles in activating both the propargylic alcohol and the nitrile. The reaction was found to be general for a range of substituted propargylic alcohols with aryl and heteroaryl substiutents. The mechanism of the reaction involves the cycloaddition of CO_2 to the propargylic alcohol **423** in the presence of the copper salt and DBU yielding the *Z*-alkylidene cyclic carbonate **426** from which Cu and DBU are eliminated to furnish **427**. Hydrolysis of this carbonate results in the intermediate **428**, which then participates in a Cu-catalyzed nucleophilic attack with the nitrile **429** to form **430**. Hydrolysis



Scheme 90. Synthesis of 2,4,5-trisubstituted-3(2*H*)-furanones **418**.



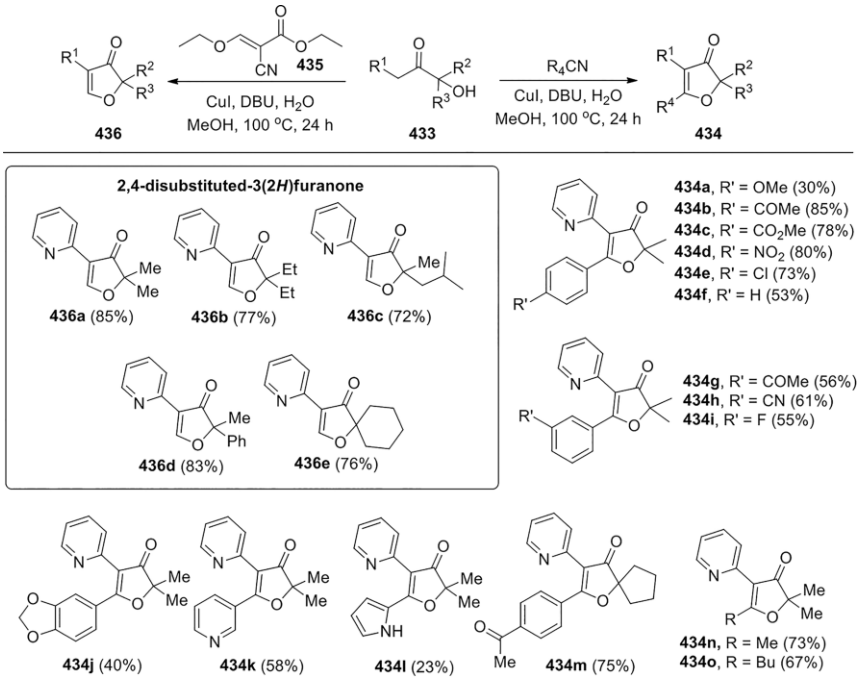
Scheme 91. CO_2-mediated Cu-catalyzed synthesis of highly substituted 3(2*H*)-furanones **424**.

of **430** provides an ester **431**, which upon intramolecular Claisen condensation and dehydration affords the 2,4,5-trisubstituted-3(2*H*)-furanones **424** as the final product.[84]

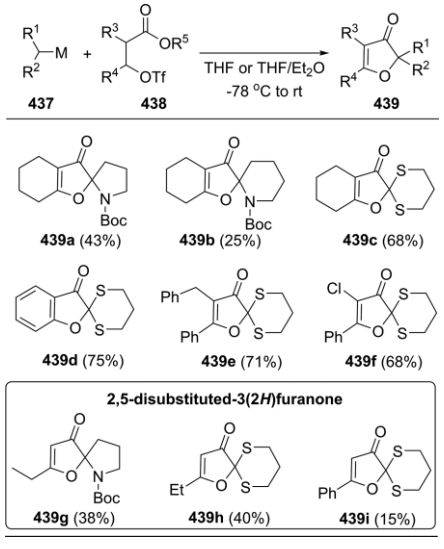
Later the same group reported a CuI/DBU mediated synthesis of a wide range of highly substituted 3(2*H*)-furanones by catalytic [4+1]annulation of α-hydroxy ketones and nitriles (Scheme 92). (Ethoxymethylene)cyanoacetate **435** was used as an HCN equivalent for the synthesis of 2,4-disubstituted-3(2*H*)-furanone **436** as well. The catalytic annulation was found to be general with different substituted arylnitriles and α-hydroxy ketones. Mechanistically, the reaction proceeds through the pathway shown in the previous scheme by the nucleophilic attack of the initially formed oxyanion species to the carbon–nitrogen triplebond of the Cu-coordinated nitrile species and then follows a similar path to afford the substituted-3(2*H*)-furanone **434**.[85]

In 2016 Dieter and co-workers published the synthesis of bis-heterocyclic spiro 3(*2H*)-furanones **439** from β-keto esters or 2-carboalkoxy phenols **438** and α-heteroatom-stabilized carbanions **437** (Scheme 93). The reaction was carried out by treating an organometallic reagent (2.0 equiv. of RMgX or RLi) and an enol or phenol triflate (2.0 equiv.) in THF (or THF/Et_2O mixture) at –78 °C to room temperature. By utilizing the developed methodology, the authors could synthesize both 2,4,5-trisubstituted and 2,5-disubstitued-3(2*H*)-furanones in moderate to good yields.[86]

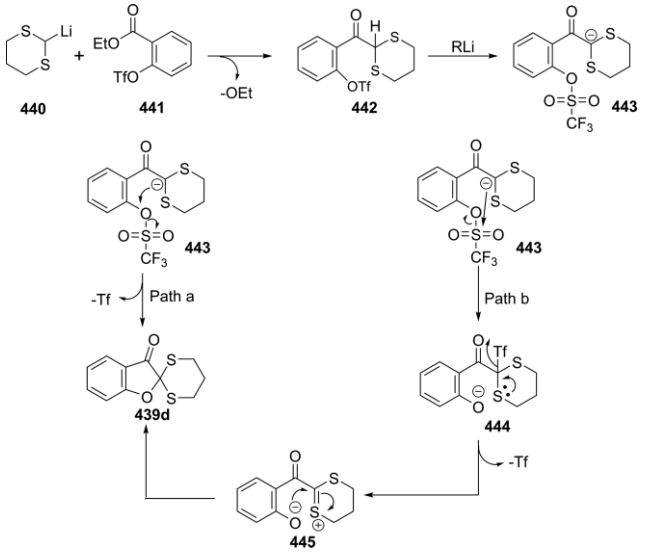
The mechanism of the above mentioned reaction starts with the nucleophilic acyl substitution by the reaction of the organolithium reagent **440** with **441** to give a ketone **442** which is then converted into an enolate **443** that attacks the oxygen atom of the triflate anion thereby furnishing the furanone **439d** directly (Path a).[86] The path b proceeds by the attack of the enolate on the sulfur atom and transfers the Tf-group from the oxygen atom to the carbon atom producing an α-trifluoromethylsulfonylketone intermediate **444**. The adjacent heteroatom (sulfur or nitrogen) can then expel the Tf-group affording a sulfenium (or iminium) cation **435**. The oxyanion subsequently undergoes a nucleophilic addition to the carbon end of the



Scheme 92. Copper-catalyzed 3(2*H*)-furanone **434** synthesis by [4+1]annulation between α-hydroxy ketones and nitriles.



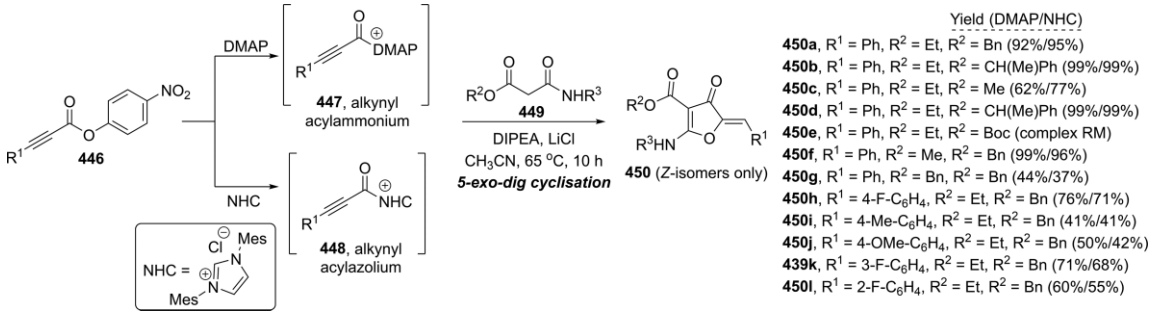
Scheme 93. Synthesis of bis-heterocyclic spiro 3(2*H*)-furanones **439** and 2,5-disubstitued-3(2*H*)-furanones.



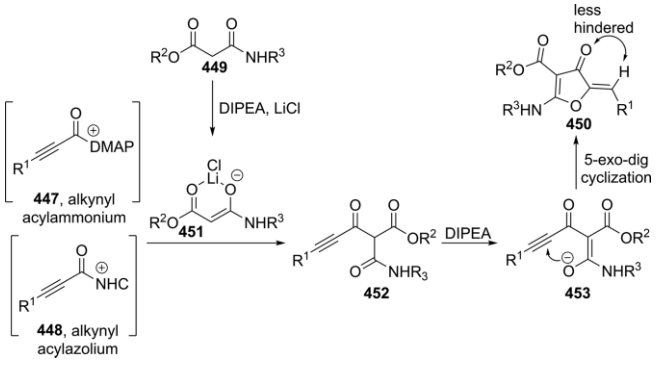
Scheme 94. Mechanism for the synthesis of heterocyclic spiro-3(2*H*)-furanone.

activated alkene furnishing the final product **439d**. Control experiments conducted by the authors supported the latter pathway (Scheme 94).

A highly regio-and stereoselective synthesis for (*Z*)-5-amino-3(2*H*)-furanone by a Lewis base/Lewis acid cooperative catalysis was developed in 2017 (Scheme 95).[87] In this report, alkynyl esters were employed **446** as precursors of α,β-unsaturated alkynyl acyl ammonium **447** and azolium precursors **448** which under cooperative catalysis conditions undergo a [2+3]annulation with amidomalonates **449** furnishing 2,4,5-trisubstituted-3(2*H*)-furanones **450**. The reaction was found to be general with a number of aryl-substitutents on the alkynyl esters and alkyl substituents on the amidomalonates. The reaction proceeds via the initial formation of the acyl ammonium intermediate **447** or acyl azolium intermediate **448** by a nucleophilic attack of the ester with DMAP or NHC.[87] The activated amidomalonate **451** generated from **449** with DIPEA/LiCl then adds to intermediates **447** or **448** in a 1,2-fashion generating **452**. The enolate anion produced from **453** by base treatment subsequently undergoes a 5-*exo-dig* cyclization to furnish the final product. The regioselectivity of the reaction was attributed to the charge distribution in the intermediates and the high stereoselectivity leading to the exclusive formation of *Z*-isomers was rationalized in terms of less steric interaction between the alkenyl hydrogen atom and the carbonyl group (Scheme 96).



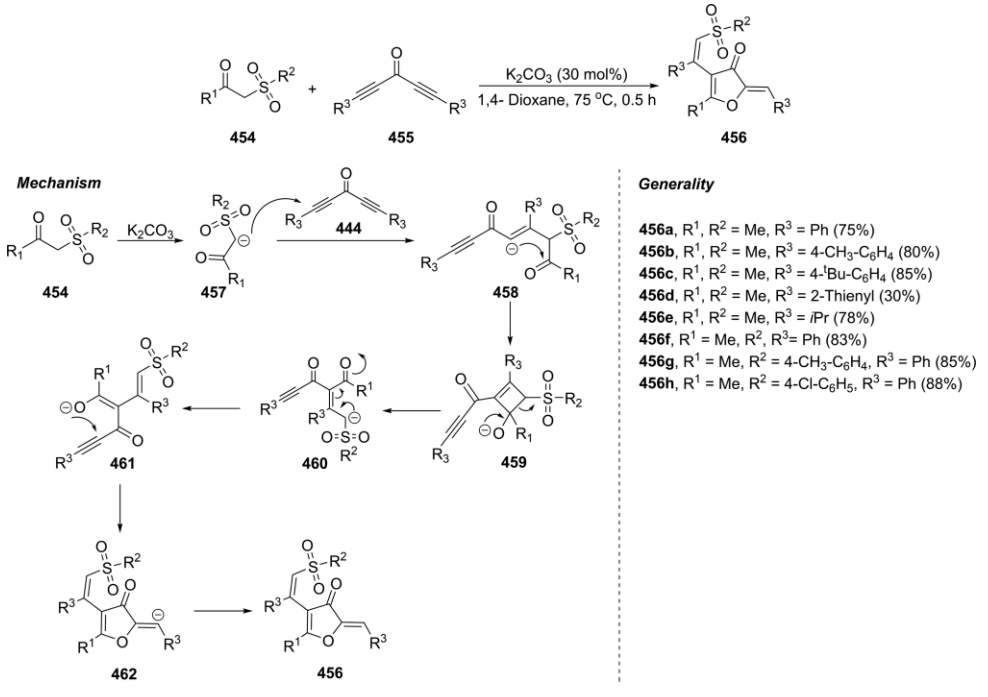
Scheme 95. Regio and stereoselective synthesis of (*Z*)-5-amino-3(2*H*)-furanones **450**.



Scheme 96. Proposed reaction pathway for the synthesis of (*Z*)-5-amino-3(2*H*)-furanones **450**.

A base promoted domino reaction of β-ketosulfones with diynones for the construction of 2,4,5-trisustituted-3(2*H*)-furanone derivatives **456** was reported recently.[88] The domino process starts with a base-induced Michael addition of the β-ketosulfones **454** to acetylenic ketones **455** generating an anion intermediate **458**. This then undergoes an intramolecular cycloaddition to furnishthe cyclobutene intermediate **459**. The ring strain of **459** induces a subsequent ring-opening yielding the oxyanion species **461** which finally undergoes an intramolecular Michael addition towards the trisubstituted-3(2*H*)-furanone ring **456** (Scheme 97). This domino sequence was found to be general with a number of substituted β-ketosulfones and diynones.

In 2018, Narsaiah and co-workers reported the synthesis of non-fluorinated **464** and fluorinated spiro-3(2*H*)-furanone derivatives **465** by a domino fluorination–defluorination approach from 1,3-diketones.[89] In this report, fluorinated spiro-3(2*H*)-furanones **465** were formed when Selectfluor was used as the fluoride source whereas non-fluorinated spiro-3(2*H*)-furanones were produced when AgF alone was used as an additive. When both reagents are employed together, 19 % of non-fluorinated and a trace amount of fluorinated product were isolated. The mechanism for the Selectfluor reaction proceeds via a difluorinated intermediate **466**. Tautomerism of **466** to the enol form results in the formation of **467**. Expulsion of a fluoride ion

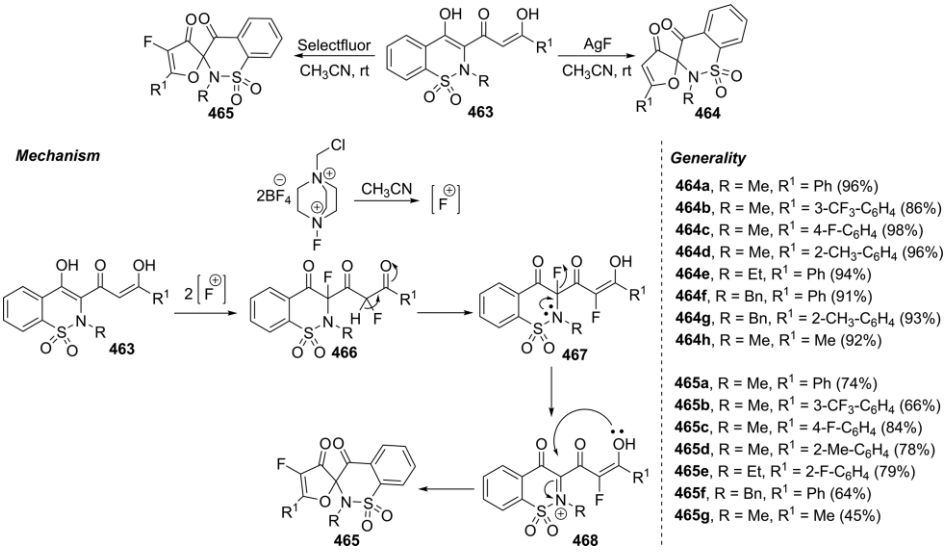


Scheme 97. Domino process for the synthesis of 2,4,5-trisubstituted-3(2*H*)-furanones **456** from β-ketosulfones with diynones.

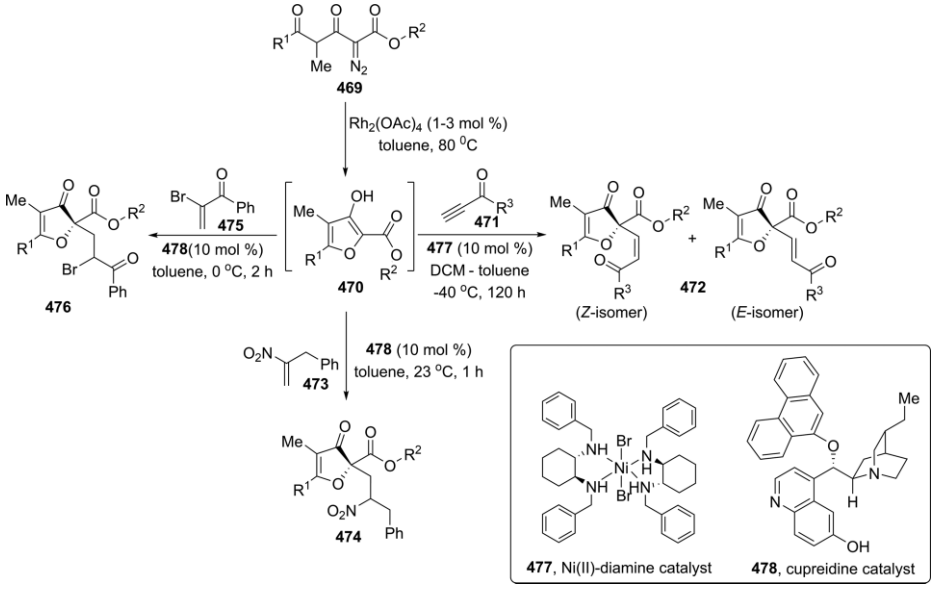
from **467** by the adjacent *N*-atom generates the iminium cation **468**. The fluorinated spiro-3(2*H*)-furanone **465** is finally produced by by an intramolecular cyclization from the enol end of the intermediate **468** (Scheme 98).

A Ni(II)–diamine complex or cupreidine catalysed the enantioselective conjugate addition of in situ generated 2-alkoxycarbonyl-3(2H)-furanones to electrophiles such as terminal alkynones, α-bromo enones, and α-benzyl nitroalkenes as reported in 2018 (Scheme 99).[90] A Rh(II)-catalyzed cyclization of the α-diazo carbonyl precursor **469** was suggested for the generation of furanone intermediate **470.** The Ni(II)–diamine complex **477** catalyzed conjugate addition of 2-alkoxycarbonyl-3(2*H*)-furanone **470** to the terminal alkynone **471** preferentially and gave the *Z*-isomer of 2,4,5-trisubstituted-3(2H)-furanone **472** in up to 79 % in yield and enantiomeric ratio (*er.*) of 98:2. The enantioselectivity of the reaction depends inversely on the temperature (*er.* = 88:12 at 23 °C, *er.* = 94:6, at –20 °C, *er.* = 98:2 at –40 °C). The enantoselective 1,4-addition of 2-alkoxycarbonyl-3(2H)-furanones with other π-electrophiles such as α-bromoenone **475** and α-benzyl nitroalkene **473** was catalyzed by a cupreidine derivative **478**. The authors utilized the Ni(II)–diamine complex catalyzed conjugate addition of 2-alkoxycarbonyl-3(*2H*)-furanone to terminal alkynone to generate a crucial intermediate **479** for the total synthesis of the natural product cephalimysin C **480**.[90] Other 1,4-adducts **481** and **483** derived from α-benzyl nitroalkenes and α-bromo enones, respectively, were utilized for synthesizing the bioactive spirocyclic-furanone-γ-lactam **482** and **484** (Scheme 100).

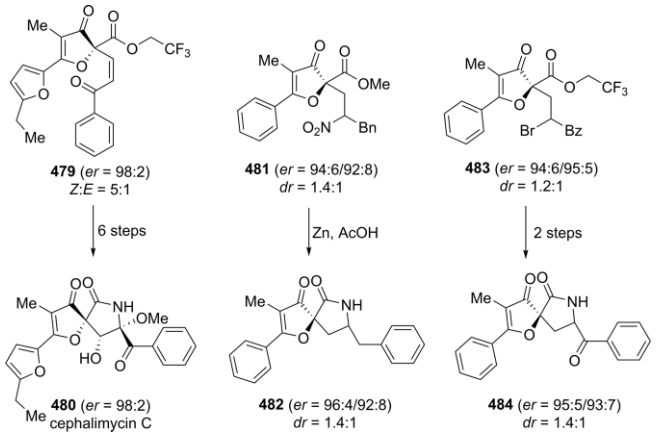
A metal-free and a Cu-catalysed syntheses of (iso)quinolinyl 3(2*H*)-furanones **487** were developed by Wang and co-workers in 2019 (Scheme 101).[91] Under copper catalysis both electron-donating and electron-withdrawing substituents on the 1,4-



Scheme 98. Plausible mechanistic pathway for the generation of fluorinated spiro 3(*2H*)-furanones **465**.



Scheme 99. Enantioselective synthesis of 2,4,5-trisubstituted-3(2*H*)-furanones.



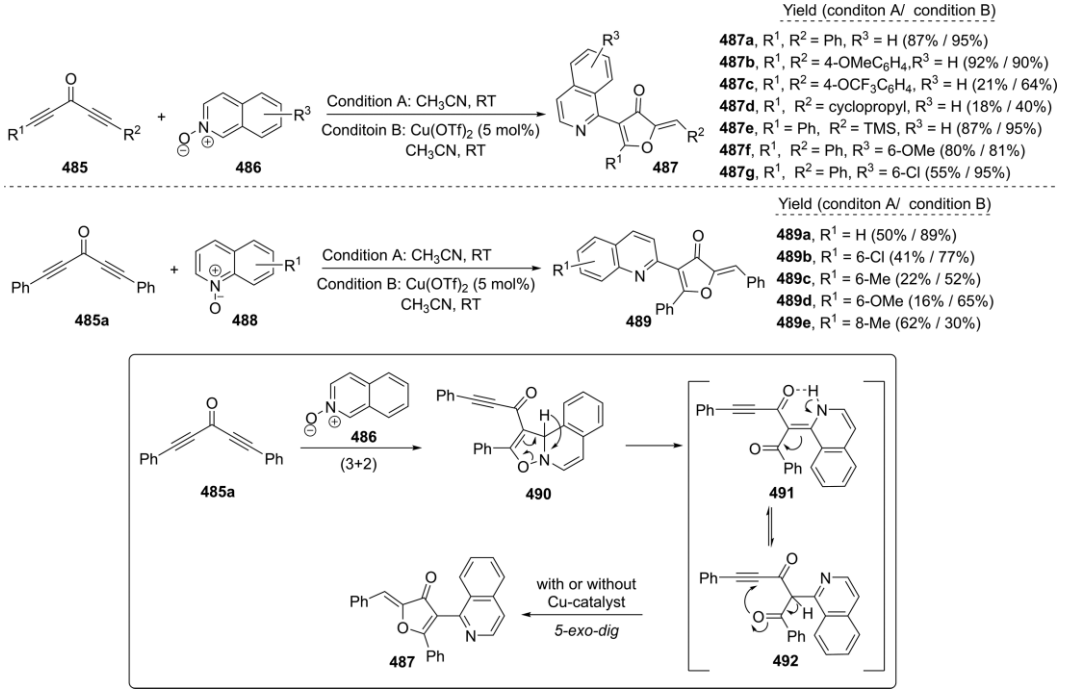
Scheme 100. Transfromation of 1,4-adducts into spirocyclicfuranone-γ-lactam.

diyn-3-ones afforded the product in good yields while under metal-free conditions a drastic substituent effect was observed on the yield. It was found that the isoquinoline derived acetylenic β-diketone cyclizes at room temperature whereas the cyclization of quinoline derived acetylenic β-diketone happens at 100 °C. This observation was attributed to the stronger basicity of isoquinoline than that of quinoline. They modified the resulting (iso)quinolinyl-3(2*H*)-furanones into (iso)-quinolinyl-isoxazoles, pyrazoles, and polycyclic (iso)quinoline derivatives. The reaction proceeded via a [3+2]cycloaddition of the *N*-oxide **486** with the electron-deficient alkyne **485** generating an intermediate **490**, which upon rearrangement and 5-*exo dig* cyclization of the acetylenic β-diketone part afforded 2,4,5-trisubstituted-3(2*H*)-furanones. The copper catalyst promoted the cyclization of **485** by activation of the carbon-carbon triple bonds, resulting in better product yields under milder conditions.

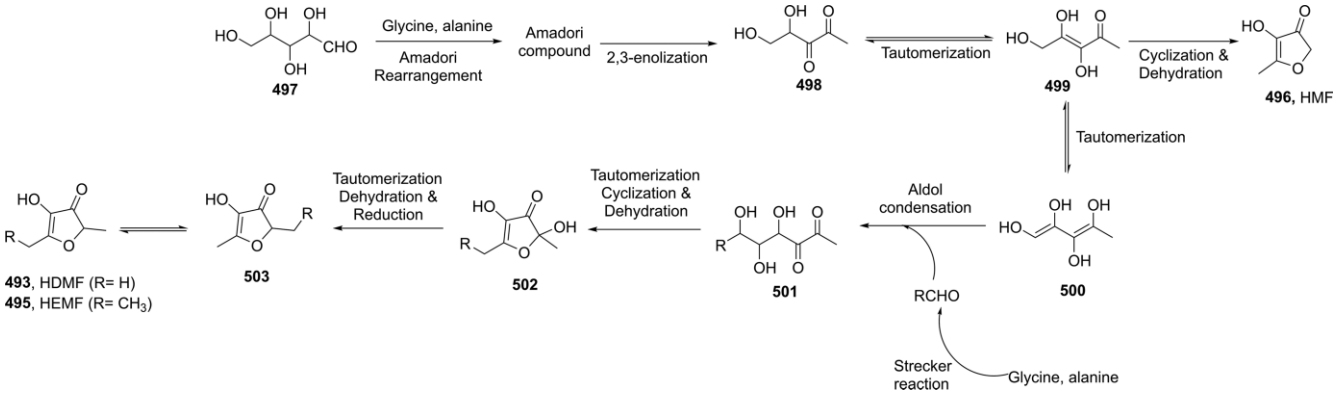
10. Biosynthesis of 3(2*H*)-furanones

As mentioned in the introduction, 3(2*H*)-furanone derivatives were found to be aroma constituents in a variety of fruits such as pineapple, strawberry, tomato, raspberry, kiwi, and mango. It has been reported that there are more than 360 volatile components known to contribute to the aroma and flavor of ripened strawberries and the most important among them are furanol or 4-hydroxy-2,5-dimethyl-3(2*H*)-furanone (HDMF) **493** and mesifuran **494** (2,5-dimethyl-4-methoxy-3(2*H*)-furanone or DMMF).[92] Other 3(2*H*)-furanone containing aroma compounds includes 4-Hydroxy-2(or 5)-ethyl-5(or 2) methyl-3(2*H*)-furanone (HEMF) **495** and 4-hydroxy-5-methyl-3(2*H*)-furanone (HMF) **496**.

The first attempt to identify the flavor components of *shoyu*, a Japanese style soy sauce was made by Tahara in 1887. Identification and isolation of 4-hydroxy-2(or 5)-ethyl-5(or 2)methyl-3(2*H*)-furanone (HEMF) **495** from *shoyu* was first reported by Nobutake Nunomuraa and co-workers in 1976 as a 3:2 tautomeric mixture.[93] It has an intense sweet odor and the authors identified HEMF as one of the major flavor components in *shoyu*. They characterized the molecule by using different spectral techniques such as NMR, IR, MS, UV, etc. The compound showed a UV absorption maximum at 290 nm due to its conjugated system. The IR spectrum showed a strong broadband at 3250 cm^{-1} indicating the presence of hydroxyl group and two strong bands at 1705 cm^{-1} and 1625 cm^{-1} were attributed to a conjugated carbonyl and an alkene respectively. They identified the different signals of the tautomers in the NMR spectra and hence calculated the tautomerism ratio based on proton intensities. Finally, comparison of the characterization data with that of the same compound synthesized by Re and co-workers[94] helped them in elucidating the structure of aroma compound in *shoyu* as a 3(2*H*)-furanone derivative. The homologues of



Scheme 101. A metal-free and a Cu-catalyzed synthesis of (iso)quinolinyl 3(2*H*)-furanones **487** and **489**.



Scheme 102. Hypothetical formation pathway of HDMF **493** and HEMF **495** from pentoses.

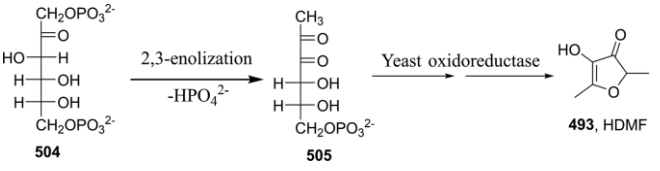
HEMF such as 4-hydroxy-2,5-dimethyl-3(2*H*)-furanone (HDMF) **493** and 4-hydroxy-5-methyl-3(2*H*)-furanone (HMF) **496** have also been isolated from *shoyu* but the concentrations are less than that of HEMF. HDMF and HMMF are formed via heat treatment of sugars and amino acids through a nonenzymatic reaction; on the other hand HEMF is produced enzymatically by *shoyu* yeast.[93]

In 1991 Sasaki and co-workers reported the biosynthesis of HEMF by yeasts. The authors suggested that HEMF was biosynthesized through the pentose-phosphate cycle. The other homologue HDMF and HMF are produced from hexoses and pentoses respectively.[95,99]

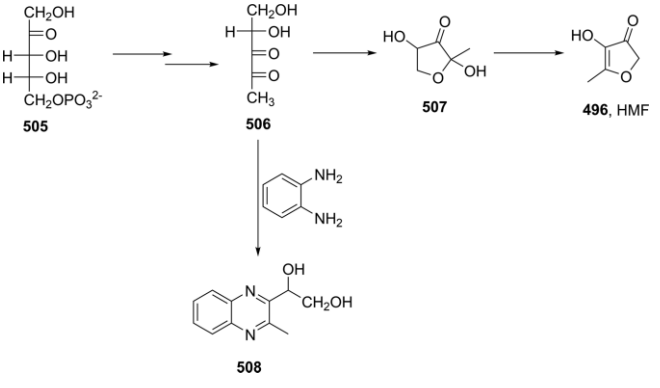
Blank and co-workers in 1996 reported that Maillard reaction of pentoses with the amino acids glycine and alanine as the main reason for the biosynthesis of HDMF and HEMF. Through their studies they identified the presence of HDMF and HEMF in Maillard reaction systems based on pentoses and the amino acids glycine and alanine through GC-MS analysis. The formation of these furanones was further supported by reactions using ^{13}C-labeled amino acids. They also identified the role of Strecker aldehydes in the furanone biosynthesis. They proposed the biosynthetic pathway as shown in Scheme 102. It was initiated by the Amadori rearrangement of pentose sugar and alanine or glycine, subsequent decomposition via 2,3-enolization forms a 1-deoxydiketose. This upon Strecker reaction followed by tautomerisation, cyclization and dehydration gave the 3(2*H*)-furanone HDMF and HEMF. Another pathway includes tautomerisation followed by aldol reaction and dehydration for the synthesis of the same from 1-deoxydiketose **501**.[96]

Schwab and co-workers in 2003 reported the biosynthesis of HDMF from D-fructose-1,6-bisphosphate **504** by the yeast *Zygosaccharo mycesrouxii* (Scheme 103). They identified the intermediate of biosynthesis as α-dicarbonyl compound **505** by a trapping reagent. They characterized the intermediate for the first time as a quinoxaline derivative. They proposed that the first step of HDMF formation by the yeast *Z. rouxii* is the formation of **505** from D-fructose-1,6-bisphosphate **504** in the culture medium followed by the enzymatic reduction mediated by an oxidoreductase of the yeast cells.[97]

The same group extended their studies on pentose-phosphateandbiosynthesisof3(2*H*)-furanonesandrevealedthata4,5-dihydroxy-2,3-pentanedione is the key intermediate in HMF biosynthesis. They detected the presence of both 4,5-dihydroxy-2,3-pentanedione and HMF in tomato fruits and suggested a similar HMF formation pathway in plants (Scheme 104). Labeling experiments and intermediate trapping supported the formation of diketone intermediates in the biosynthesis.[98]

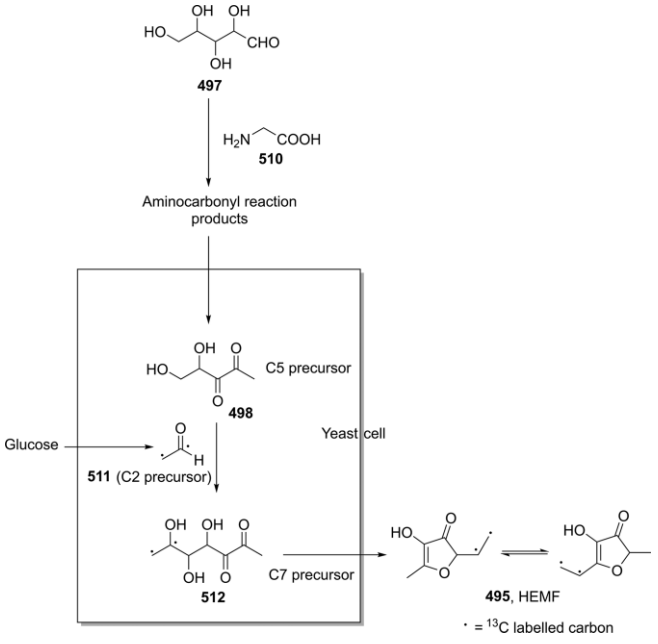


Scheme 103. Proposed bioformation of HDMF by *Z. rouxii*.



Scheme 104. Formation of HMF, 3-(1,2-dihydroxyethyl)-2-methylquinoxaline, 4,5-dihydroxy-2,3-pentanedione and from D-ribulose-5-phosphate.

Sugawara and co-workers analyzed the role of yeasts in the aminocarbonyl reaction for HEMF formation and found that it not only provides the glucose metabolite but also aids in combining the aminocarbonyl compound with the glucose metabolite (Scheme 105). They found that HEMF formation was good when yeast was cultivated in a medium where glycine concentration is high instead of alanine and also demonstrated that glucose concentration has an influence on the HEMF formation. Through their studies they confirmed the C5 precursor as aminocarbonyl reaction of ribose and glycine and C2 precursor as acetaldehyde by the glucose metabolism. They confirmed these results by ^{13}C labeling and spectral studies.[100]



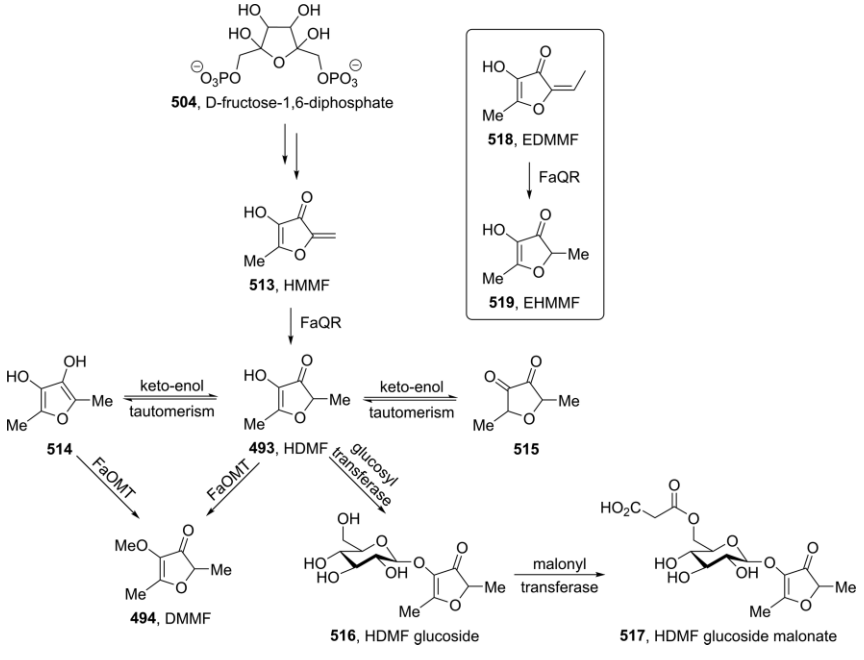
Scheme 105. Hypothetical formation of HEMF by yeast.

In 2006, Rabb et al. reported the biosynthesis of furanol and derivatives and found that it started mainly from D-fructose-1,6-diphosphate.[92] 4-Hydroxy-5-methyl-2-methylene-3(2H)-furanone (HMMF) **513** was found to form from **504** via a carbohydrate metabolism pathway (Scheme 106). The authors isolated and characterized the enzyme *Fragaria X ananassa*quinone oxidoreductase gene (FaQR) responsible for the conversion of HMMF **513** to HDMF **493**. It is from HDMF **493** that other flavor components such as mesifuran **494** and HDMF glucoside **516** are formed.

Uehara and co-workers in 2014 identified the genes involved in the formation of characteristic aromatic compound of soy sauce HEMF via gene-deletion mutants with high HEMF-production abilities by screening of the *S. cerevisiae* non-essential gene-deletion mutant collection. They identified 14 mutants with high HEMF production capacities among these *adh1*Δ mutant plays a significant role. It accumulates acetaldehyde and acetaldehyde is a strong candidate for the HEMF precursor. They also found that deleting genes involved in the pentose phosphate cycle did not affect the production of HEMF. This may be either due to the non-oxidative branch of the pentose-phosphate cycle was not involved during HEMF production or HEMF was not produced using intermediates from the non-oxidative branch of the pentose-phosphate cycle. As a result, they proposed that the pentose-phosphate cycle is only partially involved in HEMF production. They extended their studies and identified the enzyme involved in the biosynthesis of the 4-hydroxy-2(or 5)-ethyl-5(or 2)-methyl-3(2H)-furanone in yeast.[101], .[102]

11. Summary and Outlook

The first report on the synthesis of 3(2*H*)-furanone derivatives appeared in 1958; after which several research groups worked and published methods for accessing this heterocycle. Initially all efforts were centered on the total synthesis of 3(2*H*)-furanone containing natural products. The interesting biological properties exhibited by these motifs fueled research on developing methods for the preparation of differently substituted 3(2*H*)-furanones. In the past four decades several new synthetic routes were reported for installing substituents at predetermined positions by starting from imaginatively designed substrates. These methods involved the use of acids or bases as



Scheme 106. Biosynthesis of furanol and other aroma imparting 3(2*H*)-furanone derivatives.

catalysts or in stoichiometric amounts, several organocatalysts and metal catalysts *etc*. Many tandem processes were also introduced for making 3(2*H*)-furanone derivatives available. Several synthetic chemists were also successful in the enantioselective synthesis of complex natural products and other substituted 3(2*H*)-furanones.

The mechanistic rationalizations of the reactions mentioned above, leave something to be desired, both from the theoretical and the experimental point of view. We believe that there is still large scope for developing new methods towards functionalized 3(2*H*)-furanones. There are many 3(2*H*)-furanone containing natural products which have not been accessed by total synthesis. By using modern computational techniques new 3(2*H*)-furanone derivatives with specific biological properties could be designed and eventually be synthesized.

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Keywords: 3(2*H*)-Furanones · Synthetic methods · Homogeneous catalysis · Cyclization · Natural products

[1] For earlier summaries of the literature, see: a) D. W. Henry, R. M. Silverstein, *J. Org. Chem.* **1966**, *31*, 2391–2394; b) Y. Li, K. J. Hale, *Org. Lett.* **2007**, *9*, 1267–1270; c) D. C. Sass, V. C. G. Heleno, J. L. C. Lopes, M. G. Constantino, *Tetrahedron Lett.* **2008**, *49*, 3877–3880.
[2] A. Husain, S. A. Khan, F. Iram, Md. A. Iqbal, M. Asif, *Eur. J. Med. Chem.* **2019**, *171*, 66–92.
[3] T. Brandt, W. I. Taylor, *J. Chem. Soc.* **1954**, 3425.
[4] a) A. B. Smith III, P. A. Levenberg, P. J. Jerris, R. M. Scarborough Jr., P. M. Wovkulich, *J. Am. Chem. Soc.* **1981**, *103*, 1501; b) P. J. Jerris, A. B. Smith III, *J. Org. Chem.* **1981**, *46*, 577; c) C. M. Marson, E. Edaan, J. M. Morrell, S. J. Coles, M. B. Hursthouse, D. T. Davies, *Chem. Commun.* **2007**, 2494–2496.
[5] T. T. Haug, S. F. Kirsch, *Synthesis and Chemistry of 3(2H)-Furanones*, Targets in Heterocyclic Systems, **2009**, *13*, p. 57–91.
[6] C. Meister, H. D. Scharf, *Synthesis* **1981**, 737–739.
[7] L. Camici, A. Ricci, M. Taddei, *Tetrahedron Lett.* **1986**, *27*, 5155–5158.
[8] F. Sher, J. L. Isidor, H. R. Taneja, R. M. Carlson, *Tetrahedron Lett.* **1973**, *14*, 577–580.
[9] H. Saimoto, M. Shinoda, S. Matsubara, K. Oshima, T. Hiyama, H. Noazki, *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3088–3092.
[10] J. Chen, R. Properzi, D. P. Uccello, J. A. Young, R. G. Dushin, J. T. Starr, *Org. Lett.* **2014**, *16*, 4146–4149.
[11] S. W. Baldwin, T. J. Mazzuckelli, *Tetrahedron Lett.* **1986**, *27*, 5975–5978.
[12] M. J. Robins, Z. Guo, M. C. Samano, S. F. Wnuk, *J. Am. Chem. Soc.* **1996**, *118*, 11317–11318.
[13] P. X. Iten, A. A. Hofmann, C. H. Eugster, *Helv. Chim. Acta* **1978**, *61*, 430–443.
[14] P. G. Baraldi, A. Barco, S. Benetti, S. Manfredini, G. P. Pollini, D. Simoni, *Tetrahedron* **1987**, *43*, 235–242.
[15] B. Varghese, S. N. Al-Busafi, F. E. O. Suliman, S. M. Z. Al-Kindy, *New J. Chem.* **2015**, *39*, 6667–6676.
[16] S. Inagaki, M. Ukaku, A. Chiba, F. Takahashi, Y. Yoshimi, T. Morita, T. Kawano, *J. Org. Chem.* **2016**, *81*, 8363–8369.
[17] S. Inagaki, K. Saito, S. Suto, H. Aihara, A. Sugawara, S. Tamura, T. Kawano, *J. Org. Chem.* **2018**, *83*, 13834–13846.
[18] K. Hirai, H. Ooi, T. Esumi, Y. Iwabuchi, S. Hatakeyama, *Org. Lett.* **2003**, *5*, 857–859.
[19] S. C. Zammit, J. M. White, M. A. Rizzacasa, *Org. Biomol. Chem.* **2005**, *3*, 2073–2074.
[20] F. Calo, J. Richardson, A. J. P. White, A. G. M. Barrett, *Tetrahedron Lett.* **2009**, *50*, 1566–1567.
[21] A. A. Rafaniello, M. A. Rizzacasa, *Org. Lett.* **2020**, *22*, 1972–1975.
[22] W. Parker, R. A. Raphael, D. I. Wilkinson, *J. Chem. Soc.* **1958**, 3871–3875.
[23] H. G. Lehmann, *Angew. Chem. Int. Ed. Engl.* **1965**, *4*, 783; *Angew. Chem.* **1965**, *77*, 808.
[24] See ref.[4a].
[25] H. Saimoto, T. Hiyama, H. Nozaki, *J. Am. Chem. Soc.* **1981**, *103*, 4975–4977.
[26] P. J. Jerris, A. B. Smith III, *J. Org. Chem.* **1981**, *46*, 577–585.
[27] D. P. Curran, D. H. Singleton, *Tetrahedron Lett.* **1983**, *24*, 2079–2082.
[28] See ref.[9].
[29] R. F. W. Jackson, R. A. Raphael, *J. Chem. Soc., Perkin Trans. 1* **1984**, *1*, 535–539.
[30] St. Wolff, W. C. Agosta, *Tetrahedron Lett.* **1985**, *26*, 703–704.
[31] A. F. Thomas, H. Damm, *Tetrahedron Lett.* **1986**, *27*, 505–506.
[32] P. Sampson, V. Roussis, G. J. Drtina, F. L. Koerwitz, D. F. Wiemer, *J. Org. Chem.* **1986**, *51*, 2525–2529.
[33] Y. Inoue, K. Ohuchi, I.-F. Yen, S. Imaizumi, *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3518–3522.
[34] Y. Inoue, K. Ohuchi, S. Imaizumi, H. Hagiwara, H. Uda, *Synth. Commun.* **1990**, *20*, 3063–3068.
[35] S. Manfredini, P. G. Baraldi, R. Bazzanini, M. Guarnen, D. Simoni, J. Balzarini, E. D. Clercq, *J. Med. Chem.* **1994**, *37*, 2401–2405.
[36] D. Villemin, P. A. Jaffrés, M. Hachémi, *Tetrahedron Lett.* **1997**, *38*, 537–538.
[37] S. Chimichi, M. Boccalini, B. Cosimelli, F. Dall'Acqua, G. Viola, *Tetrahedron* **2003**, *59*, 5215–5223.
[38] J. D. Winkler, K. Oh, S. M. Asselin, *Org. Lett.* **2005**, *7*, 387–389.
[39] a) M. Reiter, H. Turner, R. Mills-Webb, V. Gouverneur, *J. Org. Chem.* **2005**, *70*, 8478–8485; b) F. Silva, M. Reiter, R. Mills-Webb, M. Sawicki, D. Klär, N. Bensel, A. Wagner, V. Gouverneur, *J. Org. Chem.* **2006**, *71*, 8390–8394.
[40] St. F. Kirsch, J. T. Binder, C. Liébert, H. Menz, *Angew. Chem. Int. Ed.* **2006**, *45*, 5878–5880; *Angew. Chem.* **2006**, *118*, 6010.
[41] E. M. Bunnelle, C. R. Smith, S. K. Lee, S. W. Singaram, A. J. Rhodes, R. Sarpong, *Tetrahedron* **2008**, *64*, 7008–7014.
[42] Y. Liu, M. Liu, S. Guo, H. Tu, Y. Zhou, H. Gao, *Org. Lett.* **2006**, *8*, 3445–3448.
[43] H. V. K. Wangun, A. Härtl, T. T. Kiet, C. Hertweck, *Org. Biomol. Chem.* **2006**, *4*, 2545–2548.
[44] J. L. Shamshina, T. S. Snowden, *Tetrahedron Lett.* **2007**, *48*, 3767–3769.
[45] See ref.[4c].
[46] M. Ostovar, C. M. Marson, *Tetrahedron* **2013**, *69*, 6639–6647.
[47] See ref.[1b].
[48] See ref.[1c].
[49] K. C. Nicolaou, T. R. Wu, O. D. Sarlah, D. M. Shaw, E. Rowcliffe, D. R. Burton, *J. Am. Chem. Soc.* **2008**, *130*, 11114–11121.
[50] C. Du, L. Li, Y. Li, Z. Xie, *Angew. Chem. Int. Ed.* **2009**, *48*, 7853–7856; *Angew. Chem.* **2009**, *121*, 7993.
[51] M. Egi, K. Azechi, M. Saneto, K. Shimizu, S. Akai, *J. Org. Chem.* **2010**, *75*, 2123–2126.
[52] S. Al-Busafi, M. Al-Belushi, K. Al-Muqbali, *Synth. Commun.* **2010**, *40*, 1088–1092.
[53] G. Yuan, Z. He, J. Zheng, Z. Chen, H. Huang, D. Shi, C. Qi, H. Jiang, *Tetrahedron Lett.* **2011**, *52*, 5956–5959.
[54] C. Gryparis, I. N. Lykakis, C. Efe, I. P. Zaravinos, T. Vidali, E. Kladou, M. Stratakis, *Org. Biomol. Chem.* **2011**, *9*, 5655–5658.
[55] F. Hu, J. Yan, M. Cheng, Y. Hu, *Chem. Asian J.* **2013**, *8*, 482–487.
[56] T. Kusakabe, T. Takahashi, R. Shen, A. Ikeda, Y. D. Dhage, Y. Kanno, Y. Inouye, H. Sasai, T. Mochida, K. Kato, *Angew. Chem. Int. Ed.* **2013**, *52*, 7845–7849; *Angew. Chem.* **2013**, *125*, 7999.
[57] K. Chen, G. Shi, W. Zhang, H. Li, C. Wang, *J. Am. Chem. Soc.* **2016**, *138*, 14198–14201.
[58] N. Panda, D. K. Nayak, *Monatsh. Chem.* **2018**, *149*, 1093–1100.
[59] B. Göricke, M. F. Bieber, K. E. Mohr, D. Menche, *Angew. Chem. Int. Ed.* **2019**, *58*, 13019–13023; *Angew. Chem.* **2019**, *131*, 13153.
[60] M. Poonoth, N. Krause, *J. Org. Chem.* **2011**, *76*, 1934–1936.
[61] X. Dou, X. Han, Y. Lu, *Chem. Eur. J.* **2012**, *18*, 85–89.
[62] Y. Yan, R. Lu, J. Wang, Y. Xuan, M. Yan, *Tetrahedron* **2010**, *68*, 6123–6130.
[63] J. John, H. Hopf, *Eur. J. Org. Chem.* **2013**, *2013*, 841–845.

[64] J. John, E. Târcoveanu, P. G. Jones, H. Hopf, *Beilstein J. Org. Chem.* **2014**, *10*, 1462–1470.
[65] J. Zhou, L. Bai, G. Liang, Y. Chen, Z. Gan, W. Wang, H. Zhou, Y. Yu, *RSC Adv.* **2017**, *7*, 39885–39888.
[66] S. Inagaki, K. Saito, S. Suto, H. Aihara, A. Sugawara, S. Tamura, T. Kawano, *J. Org. Chem.* **2018**, *83*, 13834–13846.
[67] S. Inagaki, M. Nakazato, N. Fukuda, S. Tamura, T. Kawano, *J. Org. Chem.* **2017**, *82*, 5583–5589.
[68] J. John, V. K. Omanakuttan, T. Aneeja, C. H. Suresh, P. G. Jones, H. Hopf, *J. Org. Chem.* **2019**, *84*, 5957–5964.
[69] A. C. Day, J. Nabney, A. I. Scott, *J. Chem. Soc.* **1961**, 4067–4074.
[70] D. Taub, C. H. Kuo, N. L. Wendler, *J. Org. Chem.* **1963**, *28*, 2752–2755.
[71] G. Stork, M. Tomasz, *J. Am. Chem. Soc.* **1964**, *86*, 471–478.
[72] See ref.[1a].
[73] S. Danishefsky, F. J. Walker, *J. Am. Chem. Soc.* **1979**, *101*, 7018–7020.
[74] M. C. Pirrung, W. L. Brown, S. Rege, P. Laughton, *J. Am. Chem. Soc.* **1991**, *113*, 8561–8562.
[75] R. Antonioletti, F. Bonadies, T. Prencipe, A. Scettri, *J. Chem. Soc. Chem. Commun.* **1988**, 850–851.
[76] Q. Han, D. F. Wiemer, *J. Am. Chem. Soc.* **1992**, *114*, 7692–7697.
[77] a) T. Krummel, P. Langer, *Chem. Commun.* **2000**, 967–968; b) T. Krummel, P. Langer, *Chem. Eur. J.* **2001**, *7*, 1720–1727.
[78] a) J. Wenke, H. Anke, O. Sterner, *Biosci. Biotechnol. Biochem.* **1993**, *57*, 961; b) Komagata, D. Fujita, S. N. Yamashita, S. Saito, T. Morino, *J. Antibiot.* **1996**, *49*, 958.
[79] Y. Hayashi, M. Shoji, S. Yamaguchi, T. Mukaiyama, J. Yamaguchi, H. Kakeya, H. Osada, *Org. Lett.* **2003**, *5*, 2287–2290.
[80] B. Crone, S. F. Kirsch, *J. Org. Chem.* **2007**, *72*, 5435–5438.
[81] B. A. Trofimov, O. A. Shemyakina, A. G. Mal'kina, I. A. Ushakov, O. N. Kazheva, G. G. Alexandrov, O. A. Dyachenko, *Org. Lett.* **2010**, *12*, 3200–3203.
[82] O. A. Shemyakina, A. V. Stepanov, O. G. Volostnykh, A. G. Mal'kina, I. A. Ushakov, B. A. Trofimov, *Russ. J. Org. Chem.* **2014**, *50*, 1617–1620.
[83] O. G. Volostnykh, O. A. Shemyakina, A. V. Stepanov, I. A. Ushakov, T. N. Borodina, *Synthesis* **2018**, *50*, 4905–4914.
[84] C. Qi, L. Huang, G. Yuan, Y. Ren, H. Jiang, *Org. Lett.* **2011**, *13*, 5520–5523.
[85] H. He, C. Qi, X. Hu, L. Ouyang, W. Xiong, H. Jiang, *J. Org. Chem.* **2015**, *80*, 4957–4965.
[86] A. Picado, S. J. Li, R. K. Dieter, *J. Org. Chem.* **2016**, *81*, 1391–1400.
[87] J. Cao, K. Sun, S. Dong, T. Lu, Y. Dong, D. Du, *Org. Lett.* **2017**, *19*, 6724–6727.
[88] W. Tong, Q. Li, Y. Xu, H. Wang, Y. Chen, Y. Pana, *Adv. Synth. Catal.* **2017**, *359*, 4025–4035.
[89] D. K. Swaroop, N. R. Kumar, P. Nagender, G. J. Dev, N. J. Babu, B. Narsaiah, *Eur. J. Org. Chem.* **2018**, 413–417.
[90] P. Vojackova, D. Chalupa, J. Prieboj, M. Necas, J. Svenda, *Org. Lett.* **2018**, *20*, 7085–7089.
[91] X. Li, T. Wang, Z. Zhang, *Adv. Synth. Catal.* **2019**, *361*, 696–701.
[92] T. Raab, J. A. Lo'pez-Ráez, D. Klein, J. L. Caballero, E. Moyano, W. Schwab, J. Muñoz-Blancob, *Planta Cell* **2006**, *18*, 1023–1037.
[93] N. Nunomuraa, M. Sasakia, Y. Asaoa, T. Yokotsukaa, *Agric. Biol. Chem.* **1976**, *40*, 491–495.
[94] L. Re, B. Maurer, G. Ohlofl', *Helv. Chim. Acta* **1973**, *56*, 1882.
[95] M. Sasaki, N. Nunomura, T. Matsudo, *J. Agric. Food Chem.* **1991**, *39*, 934–938.
[96] I. Blank, L. B. Fay, *J. Agric. Food Chem.* **1996**, *44*, 531–536.
[97] T. Hauck, F. Bruhlmann, W. Schwab, *Appl. Environ. Microbiol.* **2003**, *69*, 3911–3918.
[98] T. Haucka, Y. Hubnera, F. Bruhlmannb, W. Schwab, *Biochim. Biophys. Acta Gen. Subj.* **2003**, *1623*, 109–119.
[99] J. C. Slaughter, *Biol. Rev.* **1999**, *74*, 259–276.
[100] M. Ohata, K. Kohama, Y. Morimitsu, K. Kubota, E. Sugawara, *Biosci. Biotechnol. Biochem.* **2007**, *71*, 407–413.
[101] K. Uehara, J. Watanabe, T. Akao, D. Watanabe, Y. Mogi, H. Shimoi, *Appl. Environ. Mlicrobiol.* **2014**, DOI:https://doi.org/10.1128/AEM.02628-14.
[102] K. Uehara, J. Watanabe, Y. Mogi, Y. Tsukioka, *J. Biosci. Bioeng.* **2016**, DOI:https://doi.org/10.1016/j.jbiosc.2016.10.004.

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Tandem α-Arylation/Cyclization of 4-Haloacetoacetates with Arynes: A Metal-Free Approach toward 4-Aryl-3-(2*H*)-furanones

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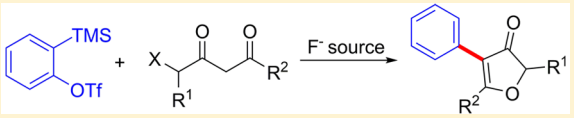
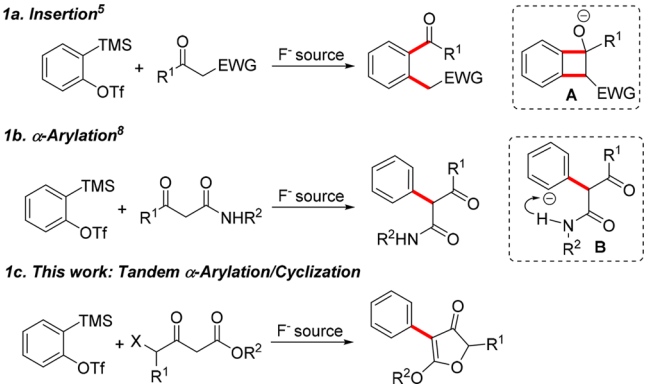
Supporting Information

ABSTRACT: An efficacious, metal-free strategy has been developed for the synthesis of 4-aryl-3-(2*H*)-furanones. The reaction proceeds via the nucleophilic addition of an active methylene compound to the aryne followed by ring closing of the adduct. The reaction proceeds under mild conditions, is applicable for gram-scale synthesis of 4-aryl-3-(2*H*)-furanones, and is general for a range of substituted arynes and haloacetates.



The chemistry of arynes[1] and the associated primarily metal-free methodologies[2] have been in the limelight since the introduction of their fluoride-induced generation from *o*-silyl aryltriflates.[3] These highly reactive intermediates have been skillfully utilized in a variety of cycloadditions,[4] insertions,[5] and multicomponent reactions[6] and also in the total synthesis of natural products.[7] The extreme reactivity of arynes can be attributed to factors such as high electrophilicity (associated with the low-lying LUMO) and the strained carbon−carbon triple bond. These features have also triggered research on the reactivity of neutral nucleophiles toward arynes, which has resulted in excellent methodologies for arylation.[1] In contrast, the addition of 1,3-diactivated methylene species across the aryne carbon−carbon triple bond have led to the generation of 1,2-disubstituted arenes via an insertion pathway.[5] Tambar and Stoltz first reported the insertion of β-ketoesters into arynes which proceeded through a formal [2 + 2] cycloaddition/fragmentation cascade via the benzocyclobutene intermediate **A** (Scheme 1a).[5b] Later, several groups reported the insertion of different 1,3-diactivated methylene species such as cyanomethyldiphenylphosphine oxide,[5c] *p*-toleuenesulfonylacetonitrile,[5d] β-keto sulfones,[5e] or β-ketophosphonates[5f] into arynes (Scheme 1a). C-Arylation of 1,3-dicarbonyl compounds with arynes was effected by the groups of Mhaske and Rodriguez (Scheme 1b).[8] They used malonamides[8a] and β-ketoamides[8b] which participated in an α-arylation by exploiting the presence of a secondary amide NH proton which transfers quickly to the intermediate aryl anion **B** (Scheme 1b), thereby preventing the insertion of arynes with 1,3-dicarbonyls. Recently, Mohanan and co-workers reported a decarbethoxylative arylation strategy employing arynes and fluoromalonamates toward α-aryl-α-fluoroacetamides.[9]

Scheme 1. Reactions of 1,3-Dicarbonyl Compounds with Arynes: Insertion vs Arylation



The 3-(2*H*)-furanone moiety is found as a core structure in many natural products, e.g., in bullatenone, jatrophone, and geiparvarin.[10] Furthermore, a wide range of biological properties such as antiulcer, antiallergic, anti-inflammatory, and antitumor activities have been reported for substituted 3-(2*H*)-furanones, which makes them interesting targets for organic and medicinal chemists.[11] The known synthetic routes toward this heterocyclic motif include transformations of substituted furans, cyclizations of α-hydroxy-1,3-diketones and allenic hydroxy ketones, and transition-metal and organo-

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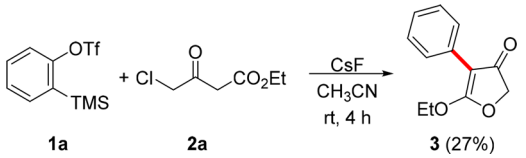
catalyzed protocols.[10c,12] Recently, we have also reported on the synthesis of 4-substituted 3-(2*H*)-furanones by the Pd-catalyzed reaction of 4-haloacetoacetates with activated alkenes, imines, and diazo compounds.[13] Inspired by the reports on the reactions of 1,3-diactivated methylene species and arynes and reflecting our continued interest in the development of synthetic protocols toward 4-substituted 3-(2*H*)-furanones, we speculated that a reaction of 4-haloacetoacetate with an aryne would result in a new methodology for accessing 4-aryl-3-(2*H*)-furanones via a tandem α-arylation/cyclization pathway (Scheme 1c).

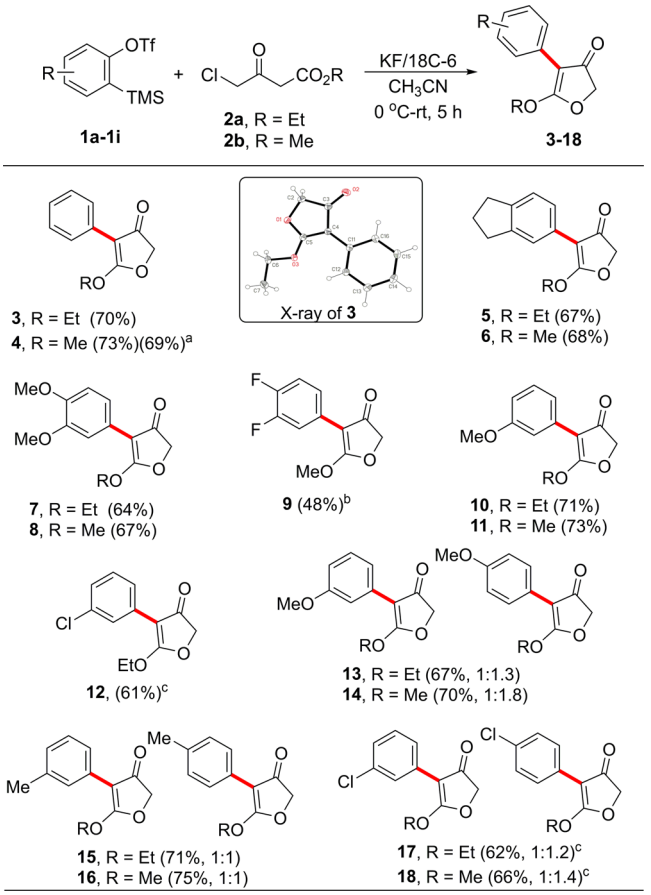
We initiated the investigations with 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **1a** and ethyl 4-chloroacetoacetate **2a** as substrates. The first reaction of **1a** with **2a** was performed in the presence of 5 equiv of CsF (which is the F^- source for the generation of benzyne and also a base) in CH_3CN at room temperature. As expected, 4-phenyl-3-(2*H*)-furanone **3** was isolated from the reaction in 27% yield after 4 h (Scheme 2).

Scheme 2. Synthesis of 4-Aryl-3-(2*H*)-furanone from Benzyne and 4-Chloroacetoacate



The optimization of the reaction conditions was continued with **1a** and **2a** and was found to be a combination of 1.25 equiv of benzyne precursor, 1.0 equiv of 4-haloacetoacetate, and 5.0 equiv of KF/18-C-6 in CH_3CN at 0 °C with subsequent stirring at room temperature for 5 h.[14] These optimized conditions for the tandem α-arylation/cyclization methodology were utilized for studying the generality of differently substituted arynes (Table 1). Both ethyl **2a** and methyl acetoacetates **2b** participated in the cascade reaction with simple benzyne affording the corresponding 4-phenyl-furanones **3** and **4** in 70% and 73% yields, respectively. The compound **4** was also made on a gram scale and obtained in good yields (69%). The reactions of **2a** and **2b** with 6-(trimethylsilyl)-2,3-dihydro-1*H*-inden-5-yl triflate afforded the expected products **5** and **6** in good yields. Disubstituted aryne precursors such as 4,5-dimethoxy-*o*-silylphenyl triflate and 4,5-difluoro-*o*-silylphenyl triflate also participated in the tandem reaction with 4-haloacetoacetates furnishing the 4-arylated furanones **7**–**9** in moderate to good yields. Importantly, the reaction of 4,5-difluoro-*o*-silylphenyl triflate was found to be complete in 2 h at 0 °C. Interestingly, the fluoride-induced tandem reaction of 3-methoxy-1,2-benzyne with **2a** and **2b** afforded furanones **10** and **11** as single regioisomers and in good yields. High regiospecificity was also observed in the reaction between 3-chloro-1,2-benzyne and ethyl 4-chloroacetoacetate **2a**, wherein the product **12** was isolated in 61% yield. Nevertheless, the reactions of some other 4-substituted 1,2-benzynes with 4-chloroacetoacetates afforded an inseparable mixture of regioisomers. In the case of 4-methoxybenzyne, the products **13** and **14** were obtained as a mixture of regioisomers in ratios 1:1.3 and 1:1.8, respectively, whereas, the reactions of **2a** and **2b** with 4-methylbenzyne afforded the products **15** and **16** in good yields but as 1:1 regioisomeric mixtures. The reactions of 4-chlorobenzyne with **2a** and **2b** also afforded the corresponding substituted furanones **17** and **18** as mixtures of regioisomers and in slightly lower yields than the former.

Table 1. Generality of 4-Aryl-3-(2*H*)-furanone Synthesis with Various Arynes*



*Reaction conditions: **1** (1.25 equiv), **2** (1.0 equiv), KF (5.0 equiv), 18-C-6 (5.0 equiv), CH_3CN (4.0 mL), 0 °C to rt, 5 h. [a]Started with 1.0 g of **2b**, [b]0 °C, 2 h. [c]0 °C, 4 h.

We then turned our attention to varying the 4-haloacetoacetate part and thus chose ethyl 4-bromo-3-oxopentanoate **2c** with the idea of introducing a methyl group at the second position of the 3(2*H*)-furanone moiety (Table 2). The reaction was found to work well with simple benzyne, which afforded the 2-methyl-4-phenyl-3(2*H*)-furanone **19** in 69% yield. A 1.2:1 regioisomeric mixture of substituted furanones **20** was obtained in good yield by the reaction of **2c** with 4-methylbenzyne. However, our attempt to introduce two methyl groups at the second position of 3(2*H*)-furanone with ethyl 4-bromo-4-methyl-3-oxopentanoate **2d** was unsuccessful (intractable reaction mixture) even on heating.

Our next effort was to check the reactivity of 4-bromo-3-oxo-*N*-phenylbutanamide **2e** toward the present tandem reaction. The reactions with unsubstituted benzyne (**1a**) and dimethoxybenzyne (**1c**) afforded substituted furanones **22** and **23** in moderate yields. To our dismay, the reaction of 1-bromopentane-2,4-dione **2f** failed to furnish the expected product **24** under the optimized conditions.

A plausible mechanism for the formation of 4-aryl-3-(2*H*)-furanone (Figure 1) is computed using M06L/SMD/6-311G(d,p) level density functional theory (SI). The fluoride-

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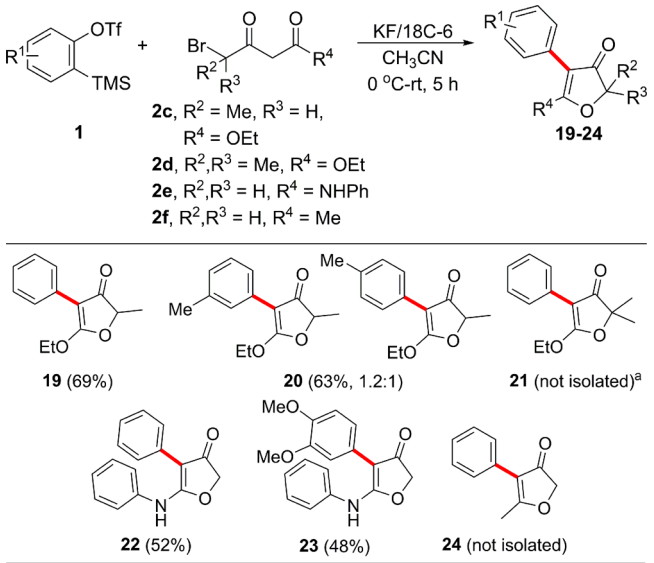
J. Org. Chem. 2019, 84, 5957–5964

Table 2. Generality of 4-Aryl-3-(2*H*)-furanone Synthesis with Various 4-Haloacetoacates*

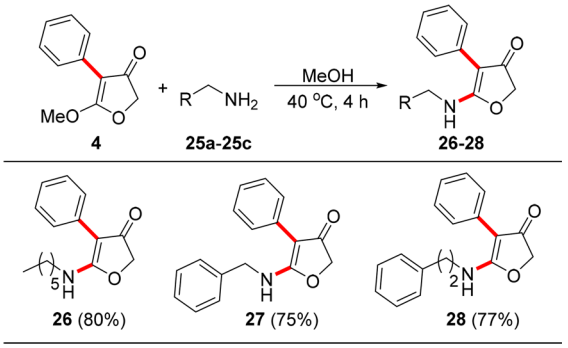


*Reaction conditions: **1** (1.25 equiv), **2** (1.0 equiv), KF (5.0 equiv), 18-C-6 (5.0 equiv), CH_3CN (4.0 mL), 0 °C to rt, 5 h. [a]60 °C, 6 h.

induced formation of enolate (**a** to **b** via **TS1**) is nearly barrierless, and the subsequent formation of the anionic benzyne adduct **c** is spontaneous and highly exothermic. Similarly, the proton abstraction from HF by the aryl anion **c** has to take place instantaneously due to the formation of the highly exothermic product **d**, the arylated ester−fluoride ion complex. At this stage, F^- anion abstracts the proton from the remaining C−H bond to form the arylated enolate−HF complex (**e**). The transition state **TS2** for this reaction suggests a barrier height of 4.0 kcal/mol. The enolate **f** undergoes an intramolecular cyclization through the formation of an S_N2-type transition state **TS3** to yield the final product in association with the leaving group Cl^- (**g**). The activation barrier for the cyclization is 13.1 kcal/mol, and the exothermic character of the overall reaction is 102.0 kcal/mol.

Finally, we tried to synthetically modify the 3(2*H*)-furanone skeleton by introducing amine functions at the fifth position. These heterocyclic analogues of prostaglandins[15] were synthesized by treating furanones with various amines in MeOH at 40 °C for 4 h. From all of the reactions, the corresponding azaprostaglandin analogues were isolated in good to excellent yields (Scheme 3).

Scheme 3. Synthesis of Heterocyclic Analogues of Prostaglandins from 4-Aryl-3-(2*H*)-furanone 4[a]



[a]Reaction conditions: **4** (1.0 equiv), **25** (1.05 equiv), MeOH (2.0 mL), 40 °C, 4 h.

In conclusion, we have developed a tandem process for the synthesis of 4-aryl-3-(2*H*)-furanone from benzyne and 4-

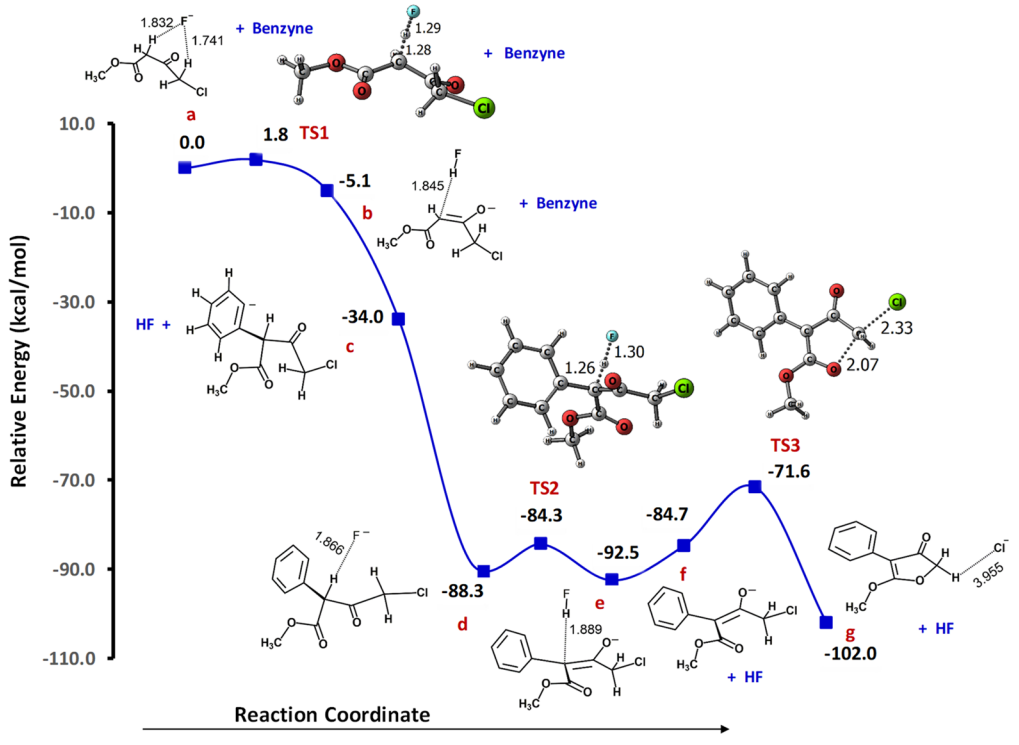


Figure 1. Energy profile for the mechanism of the formation of 4-aryl-3-(2*H*)-furanone.

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haloacetoacetates. The reaction was found to be general toward a variety of substituted arynes, and in some cases, regiospecificity was observed. The reaction proceeds via a tandem α-arylation−intramolecular cyclization pathway. We have shown that additional substituents can be introduced to the second or fifth position of the 3(2*H*)-furanone moiety by using appropriately substituted 4-halo-1,3-diketo compounds. Finally, different heterocyclic analogues of prostaglandins were synthesized from 4-phenyl-3(2*H*)-furanone. We are currently investigating the effect of substituents on the activated carbon of 4-haloacetoacetates, and the results will be reported in due course.

EXPERIMENTAL SECTION

General Experimental Methods. All chemicals were of the best grade commercially available and were used without further purification. Benzyne precursors 2-(trimethylsilyl)phenyl triflate **1a**, 4,5-dimethoxy-2-(trimethylsilyl)phenyl triflate **1c**, 3-methoxy-2-(trimethylsilyl)phenyl triflate **1e**, 4-methyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **1h**, and 4-methoxy-2-(trimethylsilyl)phenyl triflate **1g** were purchased from TCI Chemicals. Benzyne precursor 2-chloro-6-(trimethylsilyl)phenyl triflate **1f**, ethyl 4-chloroacetoacetate **2a**, methyl 4-chloroacetoacetate **2b**, CsF, KF, 18-C-6, and TBAF were purchased from Sigma-Aldrich. Benzyne precursors 6-(trimethylsilyl)-indan-5-yl triflate **1b**, 4,5-difluoro-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **1d**, and 4-chloro-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **1i** were purchased from ABCR chemicals. 4-Bromoacetoacetates were prepared by the following reported procedures.[16] All solvents were purified according to the standard procedures; dry solvents were obtained according to the literature methods and stored over molecular sieves. Analytical thin-layer chromatography was performed on polyester sheets precoated with silica gel containing fluorescent indicator (POLYGRAMSIL G/UV254). Gravity column chromatography was performed using silica gel, and mixtures of hexanes/ethyl acetate were used for elution. Melting points were measured with a Büchi 530 melting point apparatus and are uncorrected. NMR spectra were recorded with Bruker Avance-300 (300 MHz for ^{1}H NMR, 75 MHz for ^{13}C{^{1}H} NMR), Bruker DRX-400 (400.1 MHz for ^{1}H NMR, 100.6 MHz for ^{13}C{^{1}H} NMR) and Bruker AMX-500 (500 MHz for ^{1}H NMR, 125 MHz for ^{13}C{^{1}H} NMR) instruments. All spectra were measured at 300 K, unless otherwise specified. The chemical shifts δ are given in ppm and referenced to the external standard TMS or internal solvent standard. ^{1}H NMR coupling constants (J) are reported in Hertz (Hz), and multiplicities are indicated as follows s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublets). Mass spectra were performed with a ThermoFinnigan MAT95XL, a ThermoFisher Scientific LTQ Orbitrap Velos, and an Agilent 6890 gas chromatograph with JMS-T100GC spectrometer or with a ESI/HRMS at 60,000 resolution using Thermo Scientific Exactive mass spectrometer with orbitrap analyzer.

Synthesis and Characterization of 4-Aryl-3(2*H*)-furanones. *5-Ethoxy-4-phenylfuran-3(2H)-one (**3**).* Following the general experimental procedure with 2-(trimethylsilyl) phenyl trifluoromethanesulfonate **1a** (227 mg, 1.25 equiv), ethyl 4-chloroacetoacetate **2a** (100 mg, 0.61 mmol), KF (177 mg, 5.0 equiv), and 18-C-6 (806 mg, 5.0 equiv) in CH_3CN (4.0 mL) at 0 °C and subsequent stirring at room temperature for 5 h. The crude product was purified by silica gel (100−200 mesh) column chromatography (30% ethyl acetate in hexanes) to afford the desired product **3** as a pale brown solid (87 mg, 70%). Analytical data of **3**: Mp: 104−106 °C. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.80−7.77 (m, 2H), 7.31−7.26 (m, 2H), 7.15−7.10 (m, 1H), 4.61 (s, 2H), 4.52 (q, 2H, J = 9.0 Hz), 1.45 (t, 3H, J = 9.0 Hz) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 194.1, 180.6, 129.5, 128.2, 126.0, 125.9, 93.9, 74.6, 66.6, 14.8 ppm. HRMS (EI) m/z: $(M)^+$ calcd for $C_{12}H_{12}O_3$ 204.0786, found 204.0797.

*5-Methoxy-4-phenylfuran-3(2H)-one (**4**).* Following the general experimental procedure with 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **1a** (248 mg, 1.25 equiv), methyl 4-chloroacetoacetate **2b** (100 mg, 0.66 mmol), KF (192 mg, 5.0 equiv), and 18-C-6 (872 mg, 5.0 equiv) in CH_3CN (4.0 mL) at 0 °C and subsequent stirring at room temperature for 5 h. The crude product was purified by silica gel (100−200 mesh) column chromatography (30% ethyl acetate in hexanes) to afford the desired product **4** as an off-white solid (92 mg, 73%). For the gram-scale preparation of **4**, the yield was 69% (1.29 g). Analytical data of **4**. Mp: 59−61 °C. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.78−7.75 (m, 2H), 7.31−7.26 (m, 2H), 7.15−7.10 (m, 1H), 4.62 (s, 2H), 4.12 (s, 3H) ppm. ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 194.1, 180.8, 129.2, 128.2, 126.1, 126.0, 94.1, 74.7, 56.7 ppm. HRMS (EI) m/z: $(M)^+$ calcd for $C_{11}H_{10}O_3$ 190.0624, found 190.0628.

*4-(2,3-Dihydro-1H-inden-5-yl)-5-ethoxyfuran-3(2H)-one (**5**).* Following the general experimental procedure with 6-(trimethylsilyl)-indan-5-yl triflate **1b** (258 mg, 1.25 equiv), ethyl 4-chloroacetoacetate **2a** (100 mg, 0.61 mmol), KF (177 mg, 5.0 equiv), and 18-C-6 (806 mg, 5.0 equiv) in CH_3CN (4.0 mL) at 0 °C and subsequent stirring at room temperature for 5 h. The crude product was purified by silica gel (100−200 mesh) column chromatography (30% ethyl acetate in hexanes) to afford the desired product **5** as a pale yellow solid (99 mg, 67%). Analytical data of **5**. Mp: 70−72 °C. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.63 (s, 1H), 7.51−7.47 (m, 1H), 7.16−7.13 (d, 1H, J = 6.0 Hz), 4.59 (s, 2H), 4.49 (q, 2H, J = 6.0 Hz), 2.87−2.79 (m, 4H), 2.03−1.93 (m, 2H), 1.43 (t, 3H, J = 6.0 Hz) ppm. ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): 194.3, 180.5, 144.1, 142.1, 127.0, 124.1, 124.1, 122.2, 94.4, 74.5, 66.5, 33.0, 32.7, 25.5, 14.9. ppm. HRMS (EI) m/z: $(M)^+$ calcd for $C_{15}H_{16}O_3$ 244.1094, found 244.1086.

*4-(2,3-Dihydro-1H-inden-5-yl)-5-methoxyfuran-3(2H)-one (**6**).* Following the general experimental procedure with 6-(trimethylsilyl)-indan-5-yl triflate **1b** (279 mg, 1.25 equiv), methyl 4-chloroacetoacetate **2b** (100 mg, 0.66 mmol), KF (192 mg, 5.0 equiv), and 18-C-6 (872 mg, 5.0 equiv) in CH_3CN (4.0 mL) at 0 °C and subsequent stirring at room temperature for 5 h. The crude product was purified by silica gel (100−200 mesh) column chromatography (30% ethyl acetate in hexanes) to afford the desired product **6** as a pale yellow solid (103 mg, 68%). Analytical data of **6**. Mp: 123−125 °C. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.60 (s, 1H), 7.50−7.47 (m, 1H), 7.15−7.13 (d, 1H, J = 6.0 Hz), 4.61 (s, 2H), 4.10 (s, 3H), 2.87−2.79 (m, 4H), 2.03−1.94 (m, 2H) ppm. ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 194.3, 180.7, 144.2, 142.2, 126.7, 124.2, 124.1, 122.3, 94.6, 74.6, 56.5, 33.0, 32.7, 25.5 ppm. HRMS (EI) m/z: $(M)^+$ calcd for $C_{14}H_{14}O_3$ 230.0937, found 230.0933.

*4-(3,4-Dimethoxyphenyl)-5-ethoxyfuran-3(2H)-one (**7**).* Following the general experimental procedure with 4,5-dimethoxy-2-(trimethylsilyl)phenyl triflate **1c** (273 mg, 1.25 equiv), ethyl 4-chloroacetoacetate **2a** (100 mg, 0.61 mmol), KF (177 mg, 5.0 equiv), and 18-C-6 (806 mg, 5.0 equiv) in CH_3CN (4.0 mL) at 0 °C and subsequent stirring at room temperature for 5 h. The crude product was purified by silica gel (100−200 mesh) column chromatography (30% ethyl acetate in hexanes) to afford the desired product **7** as a pale brown solid (103 mg, 64%). Analytical data of **7**. Mp: 136−138 °C. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.51 (d, 1H, J = 1.8 Hz), 7.32 (dd, 1H, J_1 = 8.4 Hz, J_2 = 2.1 Hz), 6.80 (d, 1H, J = 8.4 Hz), 4.59 (s, 2H), 4.51 (q, 2H, J = 7.2 Hz), 3.84 (s, 3H), 3.81 (s, 3H), 1.45 (t, 3H, J = 7.2 Hz) ppm. ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): 194.2, 180.2, 148.6, 147.1, 122.3, 118.4, 111.0, 109.5, 74.5, 66.5, 55.8, 55.7, 14.8 ppm. HRMS (EI) m/z: $(M)^+$ calcd for $C_{14}H_{16}O_5$ 264.0992, found 264.0984.

*4-(3,4-Dimethoxyphenyl)-5-methoxyfuran-3(2H)-one (**8**).* Following the general experimental procedure with 4,5-dimethoxy-2-(trimethylsilyl)phenyl triflate **1c** (296 mg, 1.25 equiv), methyl 4-chloroacetoacetate **2b** (100 mg, 0.66 mmol), KF (192 mg, 5.0 equiv), and 18-C-6 (872 mg, 5.0 equiv) in CH_3CN (4.0 mL) at 0 °C and subsequent stirring at room temperature for 5 h. The crude product was purified by silica gel (100−200 mesh) column chromatography (30% ethyl acetate in hexanes) to afford the desired product **8** as a brown solid (110 mg, 67%). Analytical data of **8**. Mp: 122−124 °C. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.47 (d, 1H, J = 2.1 Hz), 7.27 (dd, 1H, J_1 = 8.4 Hz, J_2 = 2.1 Hz), 6.78 (d, 1H, J = 8.4 Hz), 4.61 (s,

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J. Org. Chem. 2019, 84, 5957−5964

2H), 4.12 (s, 3H), 3.84 (s, 3H), 3.81 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 194.2, 180.5, 148.6, 147.3, 122.1, 118.5, 111.1, 109.7, 74.6, 56.7, 55.9 ppm. HRMS (EI) m/z: $(M)^+$ calcd for $C_{13}H_{14}O_5$ 250.0836, found 250.0828.

*4-(3,4-Difluorophenyl)-5-methoxyfuran-3(2H)-one (**9**).* Following the general experimental procedure with 4,5-difluoro-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **1d** (276 mg, 1.25 equiv), methyl 4-chloroacetoacetate **2b** (100 mg, 0.66 mmol), KF (192 mg, 5.0 equiv), and 18-C-6 (872 mg, 5.0 equiv) in CH_3CN (4.0 mL) at 0 °C for 2 h. The crude product was purified by silica gel (100−200 mesh) column chromatography (30% ethyl acetate in hexanes) to afford the desired product **9** as a light yellow oil (72 mg, 48%). Analytical data of **9**. TLC (SiO_2): R_f 0.26 (50% ethyl acetate in hexane). ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 7.72−7.65 (m, 1H), 7.60−7.55 (m, 1H), 7.09−7.00 (m, 1H), 4.63 (s, 2H), 4.15 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 193.6, 180.6, 121.8, 121.8, 121.8, 121.7, 117.0, 116.7, 114.7, 114.5, 92.5, 74.8, 57.0 ppm. HRMS (EI) m/z: $(M)^+$ calcd for $C_{11}H_8F_2O_3$ 226.0436, found 226.0441.

*5-Ethoxy-4-(3-methoxyphenyl)furan-3(2H)-one (**10**).* Following the general experimental procedure with 3-methoxy-2-(trimethylsilyl)phenyl triflate **1e** (250 mg, 1.25 equiv), ethyl 4-chloroacetoacetate **2a** (100 mg, 0.61 mmol), KF (177 mg, 5.0 equiv), and 18-C-6 (806 mg, 5.0 equiv) in CH_3CN (4.0 mL) at 0 °C and subsequent stirring at room temperature for 5 h. The crude product was purified by silica gel (100−200 mesh) column chromatography (30% ethyl acetate in hexanes) to afford the desired product **10** as a pale yellow solid (101 mg, 71%). Analytical data of **10**. Mp: 67−69 °C. ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 7.45−7.44 (m, 1H), 7.42−7.38 (m, 1H), 7.22−7.17 (m, 1H), 6.71−6.66 (m, 1H), 4.60 (s, 2H), 4.52 (q, 2H, J = 6.0 Hz), 3.75 (s, 3H), 1.45 (t, 3H, J = 6.0 Hz) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): 194.1, 180.6, 159.4, 130.8, 129.1, 118.4, 111.8, 111.3, 93.7, 74.6, 66.7, 55.2, 14.8. ppm. HRMS (EI) m/z: $(M)^+$ calcd for $C_{13}H_{14}O_4$ 234.0892, found 234.0882.

*5-Methoxy-4-(3-methoxyphenyl)furan-3(2H)-one (**11**).* Following the general experimental procedure with 3-methoxy-2-(trimethylsilyl)phenyl triflate **1e** (271 mg, 1.25 equiv), methyl 4-chloroacetoacetate **2b** (100 mg, 0.66 mmol), KF (192 mg, 5.0 equiv), and 18-C-6 (872 mg, 5.0 equiv) in CH_3CN (4.0 mL) at 0 °C and subsequent stirring at room temperature for 5 h. The crude product was purified by silica gel (100−200 mesh) column chromatography (30% ethyl acetate in hexanes) to afford the desired product **11** as a pale yellow solid (106 mg, 73%). Analytical data of **11**. Mp: 95−97 °C. ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 7.42−7.41 (m, 1H), 7.39−7.35 (m, 1H), 7.22−7.17 (m, 1H), 6.71−6.67 (m, 1H), 4.61 (s, 2H), 4.12 (s, 3H), 3.75 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 194.0, 180.8, 159.4, 130.6, 129.1, 118.5, 111.7, 111.5, 93.9, 74.7, 56.7, 55.2 ppm. HRMS (EI) m/z: $(M)^+$ calcd for $C_{12}H_{12}O_4$ 220.0730, found 220.0725.

*4-(3-Chlorophenyl)-5-ethoxyfuran-3(2H)-one (**12**).* Following the general experimental procedure with 2-chloro-6-(trimethylsilyl)-phenyl triflate **1f** (253 mg, 1.25 equiv), ethyl 4-chloroacetoacetate **2a** (100 mg, 0.61 mmol), KF (177 mg, 5.0 equiv), and 18-C-6 (806 mg, 5.0 equiv) in CH_3CN (4.0 mL) at 0 °C for 4 h. The crude product was purified by silica gel (100−200 mesh) column chromatography (30% ethyl acetate in hexanes) to afford the desired product **12** as a pale yellow viscous liquid (89 mg, 61%). Analytical data of **12**. TLC (SiO_2): R_f 0.37 (50% ethyl acetate in hexane). ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 7.89 (t, 1H, J = 1.5 Hz), 7.81 (d, 1H, J = 8 Hz), 7.28 (d, 1H, J = 8 Hz,), 7.16 (dd, 1H, J_1 = 7.5 Hz, J_2 = 1.0 Hz) 4.69 (s, 2H) 4.62 (q, 2H, J = 6.0 Hz) 1.54 (t, 3H, J = 6.0 Hz) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): 193.7, 180.6, 134.1, 129.4, 125.9, 125.6, 123.8, 74.7, 67.0, 14.9 ppm. HRMS (ESI): calcd for $C_{12}H_{11}ClNaO_3$ $(M + Na)^+$ 261.0289, found 261.0298.

*5-Ethoxy-4-(4-methoxyphenyl)furan-3(2H)-one and 5-Ethoxy-4-(3-methoxyphenyl)furan-3(2H)-one (**13**).* Following the general experimental procedure with 4-methoxy-2-(trimethylsilyl)phenyl triflate **1g** (250 mg, 1.25 equiv), ethyl 4-chloroacetoacetate **2a** (100 mg, 0.61 mmol), KF (177 mg, 5.0 equiv), and 18-C-6 (806 mg, 5.0 equiv) in CH_3CN (4.0 mL) at 0 °C and subsequent stirring at room temperature for 5 h. The crude product was purified by silica gel (100−200 mesh) column chromatography (30% ethyl acetate in hexanes) to afford the desired product **13** as a pale yellow solid and as regioisomers in a ratio of 1.3:1 (96 mg, 67%). Analytical data of **13**. Mp: 132−134 °C. ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 7.74−7.69 (m, 2.6H), 7.45−7.44 (m, 1H), 7.41−7.38 (m, 1H), 7.22−7.17 (m, 1H), 6.86−6.81 (m, 2.6H), 6.70−6.66 (m, 1H), 4.59 (s, 2H), 4.58 (s, 2.6H), 4.55−4.46 (m, 4.6H), 3.75 (s, 3H), 3.73 (s, 3.9H) 1.47−1.41 (m, 7H) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): 194.2, 194.0, 180.6, 180.2, 159.4, 157.7, 130.8, 129.1, 127.2, 121.9, 118.4, 113.7, 111.7, 111.3, 93.7, 93.6, 74.5, 74.5, 66.7, 66.5, 55.2, 55.1, 14.9, 14.8 ppm. HRMS (EI) m/z: $(M)^+$ calcd for $C_{13}H_{14}O_4$ 234.0892, found 234.0888.

*5-Methoxy-4-(4-methoxyphenyl)furan-3(2H)-one and 5-Methoxy-4-(3-methoxyphenyl)furan-3(2H)-one (**14**).* Following the general experimental procedure with 4-methoxy-2-(trimethylsilyl)-phenyl triflate **1g** (271 mg, 1.25 equiv), methyl 4-chloroacetoacetate **2b** (100 mg, 0.66 mmol), KF (192 mg, 5.0 equiv), and 18-C-6 (872 mg, 5.0 equiv) in CH_3CN (4.0 mL) at 0 °C and subsequent stirring at room temperature for 5 h. The crude product was purified by silica gel (100−200 mesh) column chromatography (30% ethyl acetate in hexanes) to afford the desired product **14** as a pale yellow and as regioisomers in a ratio of 1.8:1 (102 mg, 70%). Analytical data of **14**. Mp: 86−88 °C. ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 7.71−7.66 (m, 3.7H), 7.42−7.41 (m, 1H), 7.39−7.35 (m, 1H), 7.22−7.17 (m, 1H), 6.86−6.81 (m, 3.8H), 6.71−6.67 (m, 1H), 4.61 (s, 2H), 4.60 (s, 3.6H), 4.12 (s, 3H), 4.10 (s, 5.7H), 3.75 (s, 3H), 3.73 (s, 5.6H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): 194.2, 180.5, 159.5, 157.8, 130.6, 129.1, 127.3, 121.7, 118.5, 113.7, 111.7, 111.5, 93.9, 74.7, 56.6, 55.2 ppm. HRMS (ESI) m/z: $(M + H)^+$ calcd for $C_{12}H_{13}O_4$ 221.0808, found 221.0808.

*5-Ethoxy-4-(p-tolyl)furan-3(2H)-one and 5-Ethoxy-4-(m-tolyl)-furan-3(2H)-one (**15**).* Following the general experimental procedure with 4-methyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **1h** (238 mg, 1.25 equiv), ethyl 4-chloroacetoacetate **2a** (100 mg, 0.61 mmol), KF (177 mg, 5.0 equiv), and 18-C-6 (806 mg, 5.0 equiv) in CH_3CN (4.0 mL) at 0 °C and subsequent stirring at room temperature for 5 h. The crude product was purified by silica gel (100−200 mesh) column chromatography (30% ethyl acetate in hexanes) to afford the desired product **15** as a pale brown solid and as regioisomers in a ratio of 1:1 (95 mg, 71%). Analytical data of **15**. Mp: 75−77 °C. ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 7.69−7.64 (m, 2H), 7.63−7.62 (m, 1H), 7.55−7.52 (m, 1H), 7.20−7.15 (m, 1H), 7.11−7.07 (m, 2H), 6.96−6.93 (m, 1H), 4.59 (s, 2H), 4.59 (s, 2H), 4.54−4.46 (m, 4H), 2.29 (s, 3H), 2.26 (s, 3H) 1.46−1.41 (m, 6H) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): 194.2, 194.2, 180.6, 180.5, 137.7, 135.5 129.2, 128.9, 128.1, 126.8, 126.7, 126.4, 125.9, 123.1, 94.0, 93.9, 74.5, 66.6, 66.5, 21.6, 21.2, 14.8 ppm. HRMS (EI) m/z: $(M)^+$ calcd for $C_{13}H_{14}O_3$ 218.0937, found 218.0926.

*5-Methoxy-4-(p-tolyl)furan-3(2H)-one and 5-Methoxy-4-(m-tolyl)furan-3(2H)-one (**16**).* Following the general experimental procedure with 4-methyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **1h** (258 mg, 1.25 equiv), methyl 4-chloroacetoacetate **2b** (100 mg, 0.66 mmol), KF (192 mg, 5.0 equiv), and 18-C-6 (872 mg, 5.0 equiv) in CH_3CN (4.0 mL) at 0 °C and subsequent stirring at room temperature for 5 h. The crude product was purified by silica gel (100−200 mesh) column chromatography (30% ethyl acetate in hexanes) to afford the desired product **16** as a pale brown solid and as regioisomers in a ratio of 1:1 (101 mg, 75%). Analytical data of **16**. Mp: 57−59 °C. ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 7.66−7.62 (m, 2H), 7.59−7.58 (m, 1H), 7.54−7.51 (m, 1H), 7.20−7.14 (m, 1H), 7.11−7.08 (m, 2H), 6.96−6.93 (m, 1H), 4.61 (s, 2H), 4.60 (s, 2H), 4.10 (s, 3H), 4.10 (s, 3H), 2.29 (s, 3H), 2.26 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): 194.2, 194.2, 180.8, 180.7, 137.7, 135.7, 129.0, 128.9, 128.1, 126.9, 126.7, 126.2, 125.9, 123.2, 94.2, 94.0, 74.7, 56.6, 56.6, 21.6, 21.2 ppm. HRMS (EI) m/z: $(M)^+$ calcd for $C_{12}H_{12}O_3$ 204.0786, found 204.0796.

*4-(4-Chlorophenyl)-5-ethoxyfuran-3(2H)-one and 4-(3-chlorophenyl)-5-ethoxyfuran-3(2H)-one (**17**).* Following the general experimental procedure with 4-chloro-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **1i** (254 mg, 1.25 equiv), ethyl 4-chloroace-

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toacetate **2a** (100 mg, 0.61 mmol), KF (177 mg, 5.0 equiv), and 18-C-6 (806 mg, 5.0 equiv) in CH_3CN (4.0 mL) at 0 °C for 4 h. The crude product was purified by silica gel (100−200 mesh) column chromatography (30% ethyl acetate in hexanes) to afford the desired product **17** as a pale yellow oil and as regioisomers in a ratio of 1:1.2 (90 mg, 62%). Analytical data of **17**. TLC (SiO_2): R_f 0.38 (50% ethyl acetate in hexane). ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.82−7.81 (m, 1H), 7.79−7.72 (m, 3.6H), 7.26−7.19 (m, 3.4H), 7.10−7.06 (m, 1H), 4.61 (s, 2H), 4.61 (s, 2.4H), 4.58−4.40 (m, 4.4H), 1.49−1.43 (m, 6.6H) ppm. ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): 194.0, 193.8, 180.6, 180.5, 134.0, 131.3, 131.3, 129.4, 128.3, 128.0, 127.0, 125.9, 125.6, 123.7, 93.0, 92.8, 74.7, 67.1, 67.0, 14.8 ppm. HRMS (ESI) *m*/*z*: $(M)^+$ calcd for $C_{12}H_{12}ClO_3$ 239.0469, found 239.0469.

*4-(4-Chlorophenyl)-5-methoxyfuran-3(2H)-one and 4-(3-Chlorophenyl)-5-methoxyfuran-3(2H)-one (**18**).* Following the general experimental procedure with 4-chloro-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **1i** (275 mg, 1.25 equiv), methyl 4-chloroacetoacetate **2b** (100 mg, 0.66 mmol), KF (192 mg, 5.0 equiv), and 18-C-6 (872 mg, 5.0 equiv) in CH_3CN (4.0 mL) at 0 °C for 4 h. The crude product was purified by silica gel (100−200 mesh) column chromatography (30% ethyl acetate in hexanes) to afford the desired product **18** as a pale yellow oil and as regioisomers in a ratio of 1:1.4 (101 mg, 66%). Analytical data of **18**. TLC (SiO_2): R_f 0.32 (50% ethyl acetate in hexane). ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.79−7.77 (m, 1H), 7.76−7.71 (m, 3.8H), 7.25−7.17 (m, 3.8H), 7.10−7.07 (m, 1H), 4.62 (s, 2H), 4.62 (s, 2.8H), 4.14 (s, 3H), 4.13 (s, 4.2H) ppm. ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): 193.9, 193.7, 180.9, 180.8, 134.1, 131.4, 131.1, 129.4, 128.3, 127.8, 127.1, 126.0, 125.6, 123.8, 93.2, 93.0, 74.8, 56.9, 56.9 ppm. HRMS (EI) *m*/*z*: $(M)^+$ calcd for $C_{11}H_9ClO_3$ 224.0240, found 224.0252.

*5-Ethoxy-2-methyl-4-phenylfuran-3(2H)-one (**19**).* Following the general experimental procedure with 2-(trimethylsilyl) phenyl trifluoromethanesulfonate **1a** (167 mg, 1.25 equiv), ethyl 4-bromo-3-oxopentanoate **2c** (100 mg, 0.45 mmol), KF (130 mg, 5.0 equiv), and 18-C-6 (592 mg, 5.0 equiv) in CH_3CN (3.0 mL) at 0 °C and subsequent stirring at room temperature for 5 h. The crude product was purified by silica gel (100−200 mesh) column chromatography (30% ethyl acetate in hexanes) to afford the desired product **19** as a pale yellow solid (69 mg, 69%). Analytical data of **19**. Mp: 77−79 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.88 (d, 2H, J = 7.5 Hz), 7.35 (t, 2H, J = 7.5 Hz), 7.18 (t, 1H, J = 7.0 Hz), 4.74 (q, 1H, J = 7.0 Hz,), 4.58 (q, 2H, J = 7.0 Hz,), 1.57 (d, 3H, 7.0 Hz), 1.52 (t, 3H, J = 7.0 Hz,) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 196.9, 179.2, 129.8, 128.2, 125.9, 125.8, 92.4, 82.8, 66.4, 16.7, 14.8 ppm. HRMS (ESI) *m*/*z*: calcd for $C_{13}H_{14}NaO_3$, $(M + Na)^+$ 241.0835, found 241.0826.

*5-Ethoxy-2-methyl-4-(p-tolyl)furan-3(2H)-one and 5-Ethoxy-2-methyl-4-(m-tolyl)furan-3(2H)-one (**20**).* Following the general experimental procedure with 4-methyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **1h** (176 mg, 1.25 equiv), ethyl 4-bromo-3-oxopentanoate **2c** (100 mg, 0.45 mmol), KF (130 mg, 5.0 equiv), and 18-C-6 (592 mg, 5.0 equiv) in CH_3CN (3.0 mL) at 0 °C and subsequent stirring at room temperature for 5 h. The crude product was purified by silica gel (100−200 mesh) column chromatography (30% ethyl acetate in hexanes) to afford the desired product **20** as a pale yellow solid and as regioisomers in a ratio of 1.2:1 (66 mg, 63%). Analytical data of **20**. Mp: 140−142 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.76−7.73 (m, 3.2H), 7.62 (d, 1.2H, J = 8.0 Hz) 7.24 (t, 1.2H, J = 8.0 Hz), 7.16 (d, 2H, J = 8.5 Hz), 7.00 (d, 1.2H, J = 7.5 Hz,) 4.75−4.70 (m, 2.2H), 4.60−4.55 (m, 4.4H), 2.36 (s, 3.6H), 2.33 (s, 3H), 1.57 (d, 3.6H, J = 1.5 Hz), 1.56 (d, 3H, J = 1.5 Hz), 1.53−1.49 (m, 6.6H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): 197.0, 179.3, 179.1, 137.7, 135.4, 129.6, 128.9, 128.1, 126.8, 126.7, 126.7, 125.9, 123.1, 92.5, 92.4, 82.8, 66.4, 66.3, 21.6, 21.2, 16.7, 14.9. ppm. HRMS (ESI) *m*/*z*: calcd for $C_{14}H_{16}NaO_3$ $(M + Na)^+$ 255.0992, found 255.0984.

*4-Phenyl-5-(phenylamino)furan-3(2H)-one (**22**).* Following the general experimental procedure with 2-(trimethylsilyl) phenyl trifluoromethanesulfonate **1a** (148 mg, 1.25 equiv), 4-bromo-3-oxo-*N*-phenylbutanamide **2e** (100 mg, 0.39 mmol), KF (114 mg, 5.0 equiv), and 18-C-6 (516 mg, 5.0 equiv) in CH_3CN (3.0 mL) at 0 °C and subsequent stirring at room temperature for 5 h. The crude product was purified by silica gel (100−200 mesh) column chromatography (40% ethyl acetate in hexanes) to afford the desired product **22** as a pale brown solid (51 mg, 52%). Analytical data of **22**. Mp: 158−160 °C. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.43−7.38 (m, 3H), 7.37−7.36 (m, 1H), 7.35−7.32 (m, 1H), 7.30−7.29 (m, 1H), 7.28−7.26 (m, 1H), 7.24−7.20 (m, 3H), 7.15−7.09 (m, 1H), 4.65 (s, 2H) ppm. ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): 192.2, 174.9, 136.2, 130.2, 129.8, 129.8, 128.3, 127.3, 125.8, 121.8, 96.4, 75.2 ppm. HRMS (EI) *m*/*z*: calcd for $C_{16}H_{13}NO_2$ $(M)^+$ 251.0946, found 251.0941.

*4-(3,4-Dimethoxyphenyl)-5-(phenylamino)furan-3(2H)-one (**23**).* Following the general experimental procedure with 4,5-dimethoxy-2-(trimethylsilyl)phenyl triflate **1c** (175 mg, 1.25 equiv), 4-bromo-3-oxo-*N*-phenylbutanamide **2e** (100 mg, 0.39 mmol), KF (114 mg, 5.0 equiv), and 18-C-6 (516 mg, 5.0 equiv) in CH_3CN (3.0 mL) at 0 °C and subsequent stirring at room temperature for 5 h. The crude product was purified by silica gel (100−200 mesh) column chromatography (80% ethyl acetate in hexanes) to afford the desired product **23** as an amorphous solid (58 mg, 48%). Analytical data of **23**. TLC (SiO_2): R_f 0.29 (80% ethyl acetate in hexane). ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.33−7.28 (m, 3H), 7.24−7.21 (m, 2H), 7.15−7.09 (m, 1H), 6.99 (s, 1H), 6.86 (s, 2H), 4.69 (s, 2H), 3.82 (s, 6H) ppm. ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): 191.7. 174.5, 149.7, 148.1, 135.9, 129.4, 125.3, 122.2, 121.1, 119.9, 111.9, 111.9, 96.0, 74.9, 56.0 ppm. HRMS (EI) *m*/*z* calcd for $C_{18}H_{17}NO_4$ $(M)^+$ 311.1158, found 311.1152.

*5-(Hexylamino)-4-phenylfuran-3(2H)-one (**26**).* 5-Methoxy-4-phenylfuran-3(2*H*)-one **4** (100 mg, 1.0 equiv., 0.53 mmol) and *n*-hexylamine **25a** (1.1 equiv) were weighed into a dry Schlenk tube. Dry methanol (2.0 mL) was added, and the reaction mixture was stirred at 40 °C for 4 h. Upon completion of the reaction, the solvent was removed, and the residue was subjected to column chromatography on neutral alumina using hexanes/ethyl acetate mixture as eluent to afford the product **26** as a pale yellow viscous liquid (110 mg, 80%). Analytical data of **26**. TLC (SiO_2): R_f 0.23 (50% ethyl acetate in hexane). ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.42−7.38 (m, 4H), 7.22−7.20 (m, 1H), 5.63 (brs, 1H), 4.62 (s, 2H), 3.41 (m, 2H), 1.67−1.66 (m, 2H), 1.62−1.59 (m, 2H), 1.32−1.25 (m, 4H), 0.90 (t, 3H, J = 7.0 Hz) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 191.1, 176.8, 130.7, 129.2, 127.4, 126.1, 93.7, 74.5, 41.6, 31.3, 30.1, 29.7, 26.3, 22.5, 13.9 ppm. HRMS (ESI) *m*/*z*: $(M + Na)^+$ calcd for $C_{16}H_{21}NNaO_2$ 282.1465, found 282.1455.

*5-(Benzylamino)-4-phenylfuran-3(2H)-one (**27**).* 5-Methoxy-4-phenylfuran-3(2*H*)-one **4** (100 mg, 1.0 equiv., 0.53 mmol) and benzylamine **25b** (1.1 equiv) were weighed into a dry Schlenk tube. Dry methanol (2.0 mL) was added, and the reaction mixture was stirred at 40 °C for 4 h. Upon completion of the reaction, the solvent was removed and the residue was subjected to column chromatography on neutral alumina using hexanes/ethyl acetate mixture as eluent to afford the product **27** as a pale yellow viscous liquid (105 mg, 75%). Analytical data of **27**. TLC (SiO_2): R_f 0.19 (50% ethyl acetate in hexane). ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.42- 7.29 (m, 9H), 7.21−7.19 (m, 1H), 5.9 (brs, 1H), 4.65 (s, 2H), 4.60 (d, 2H, J = 6.0 Hz,) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 191.5, 176.5, 136.8, 130.4, 129.1, 129.1, 128.2, 127.5, 127.4, 126.3, 94.1, 74.6, 45.4 ppm. HRMS (ESI) *m*/*z*: $(M+Na)^+$ calcd for $C_{17}H_{15}NNaO_2$ 288.0995, found 288.0988.

*5-(Phenethylamino)-4-phenylfuran-3(2H)-one (**28**).* 5-Methoxy-4-phenylfuran-3(2*H*)-one **4** (100 mg, 1.0 equiv, 0.53 mmol) and 2-phenylethylamine **25c** (1.1 equiv) were weighed into a dry Schlenk tube. Dry methanol (2.0 mL) was added, and the reaction mixture was stirred at 40 °C for 4 h. Upon completion of the reaction, the solvent was removed, and the residue was subjected to column chromatography on neutral alumina using hexanes/ethyl acetate mixture as eluent to afford the product **28** as a pale yellow viscous liquid (114 mg, 77%). Analytical data of **28**. TLC (SiO_2): R_f 0.18 (50% ethyl acetate in hexane). ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.36- 7.19 (m, 10H), 5.58 (brs, 1H), 4.62 (s, 2H), 3.68 (q, 2H, J = 6.3 Hz,), 2.92 (t, 2H, J = 6.6 Hz,) ppm. ^{13}C{^{1}H} NMR (125 MHz,

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J. Org. Chem. 2019, 84, 5957−5964

CDCl3): δ 190.4, 176.7, 137.5, 132.2, 132.1, 132.0, 130.0, 129.1, 129.0, 128.8, 128.6, 128.5, 127.4, 127.2, 126.4, 94.5, 74.8, 42.8, 36.2 ppm. HRMS (ESI) *m/z*: $(M + Na)^+$ calcd for $C_{18}H_{17}NNaO_2$ 302.1152, found 302.1157.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.9b00488.

Optimization studies, theoretical calculations, and copies of NMR spectra for all the compounds (PDF)

X-ray crystallography data (CCDC-1891729) for **3** (CIF)

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Notes

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■ REFERENCES

(1) (a) Sanz, R. Recent Applications of Aryne Chemistry to Organic Synthesis. A Review. *Org. Prep. Proced. Int.* **2008**, *40*, 215. (b) Chen, Y., Larock, R. C. In *Modern Arylation Methods*; Ackermann, L., Ed.; Wiley-VCH: Weinheim, 2009; p 401. (c) Okuma, K. Reaction of Arynes with Carbon-Heteroatom Double Bonds. *Heterocycles* **2012**, *85*, 515. (d) Dubrovskiy, A. V.; Markina, N. A.; Larock, R. C. Use of Benzynes for the Synthesis of Heterocycles. *Org. Biomol. Chem.* **2013**, *11*, 191. (e) Wu, C.; Shi, F. A Closer Look at Aryne Chemistry: Details that Remain Mysterious. *Asian J. Org. Chem.* **2013**, *2*, 116. (f) García-López, J.-A.; Greaney, M. F. Synthesis of Biaryls Using Aryne Intermediates. *Chem. Soc. Rev.* **2016**, *45*, 6766.

(2) (a) Bhojgude, S. S.; Biju, A. T. Arynes in Transition-Metal-Free Multicomponent Coupling Reactions. *Angew. Chem., Int. Ed.* **2012**, *51*, 1520. (b) Bhunia, A.; Yetra, S. R.; Biju, A. T. Recent Advances in Transition-Metal-Free Carbon-Carbon and Carbon-Heteroatom Bond-Forming Reactions Using Arynes. *Chem. Soc. Rev.* **2012**, *41*, 3140. (c) Bhojgude, S. S.; Bhunia, A.; Biju, A. T. Employing Arynes in Diels–Alder Reactions and Transition-Metal-Free Multicomponent Coupling and Arylation Reactions. *Acc. Chem. Res.* **2016**, *49*, 1658.

(3) Himeshima, Y.; Sonoda, T.; Kobayashi, H. Fluoride-Induced 1,2-Elimination of *O*-Trimethylsilylphenyl Triflate to Benzyne Under Mild Conditions. *Chem. Lett.* **1983**, *12*, 1211.

(4) For selected reports on cycloadditions involving arynes, see: (a) Dockendorff, C.; Sahli, S.; Olsen, M.; Milhau, L.; Lautens, M. Synthesis of Dihydronaphthalenes via Aryne Diels–Alder Reactions: Scope and Diastereoselectivity. *J. Am. Chem. Soc.* **2005**, *127*, 15028. (b) Jin, T.; Yamamoto, Y. An Efficient, Facile, and General Synthesis of 1H-Indazoles by 1,3-Dipolar Cycloaddition of Arynes with Diazomethane Derivatives. *Angew. Chem., Int. Ed.* **2007**, *46*, 3323. (c) Liu, Z.; Shi, F.; Martinez, P. D. G.; Raminelli, C.; Larock, R. C. Synthesis of Indazoles by the [3 + 2] Cycloaddition of Diazo Compounds with Arynes and Subsequent Acyl Migration. *J. Org. Chem.* **2008**, *73*, 219. (d) Bhojgude, S. S.; Kaicharla, T.; Bhunia, A.; Biju, A. T. A Practical and General Diels–Alder Reaction of Pentafulvenes with Arynes. *Org. Lett.* **2012**, *14*, 4098. (e) Perez, D.; Peña, D.; Guitian, E. Cycloaddition Reactions in the Synthesis of Large Polycyclic Aromatic Compounds. *Eur. J. Org. Chem.* **2013**, *2013*, 5981. (f) Thangaraj, M.; Bhojgude, S. S.; Bisht, R. H.; Gonnade, R. G.; Biju, A. T. Diels–Alder Reaction of Tropones with Arynes: Synthesis of Functionalized Benzobicyclo[3.2.2]nonatrienones. *J. Org. Chem.* **2014**, *79*, 4757. (g) Castillo, J.-C.; Quiroga, J.; Abonia, R.; Rodriguez, J.; Coquerel, Y. The Aryne aza-Diels–Alder Reaction: Flexible Syntheses of Isoquinolines. *Org. Lett.* **2015**, *17*, 3374.

(5) For selected recent reports on insertion reactions involving arynes, see: (a) Yoshida, H.; Shirakawa, E.; Honda, Y.; Hiyama, T. Addition of Ureas to Arynes: Straightforward Synthesis of Benzodiazepine and Benzodiazocine Derivatives. *Angew. Chem., Int. Ed.* **2002**, *41*, 3247. (b) Tambar, U. K.; Stoltz, B. M. The Direct Acyl-Alkylation of Arynes. *J. Am. Chem. Soc.* **2005**, *127*, 5340. (c) Yoshida, H.; Watanabe, M.; Ohshita, J.; Kunai, A. Carbophosphinylation of Arynes with Cyanomethyldiphenylphosphine Oxide. *Chem. Lett.* **2005**, *34*, 1538. (d) Yoshida, H.; Watanabe, M.; Morishita, T.; Ohshita, J.; Kunai, A. Insertion of Arynes into Carbon–Halogen σ-Bonds: Regioselective Acylation of Aaromatic Rings. *Chem. Commun.* **2007**, *1505*, 1505. (e) Huang, X.; Xue, J. A Novel Multicomponent Reaction of Arynes, β-Keto Sulfones, and Michael-Type Acceptors: A Direct Synthesis of Polysubstituted Naphthols and Naphthalenes. *J. Org. Chem.* **2007**, *72*, 3965. (f) Liu, Y.-L.; Liang, Y.; Pi, S.-F.; Li, J.-H. Selective synthesis of O-Acylbenzylphosphonates by Insertion Reactions of Arynes into Beta-Ketophosphonates. *J. Org. Chem.* **2009**, *74*, 5691. (g) Liu, Z.; Larock, R. C. Intermolecular C–N Addition of Amides and S–N Addition of Sulfinamides to Arynes. *J. Am. Chem. Soc.* **2005**, *127*, 13112. (h) Yoshida, H.; Yoshida, R.; Takaki, K. Synchronous Ar-F and Ar-Sn Bond Formation through Fluorostannylation of Arynes. *Angew. Chem., Int. Ed.* **2013**, *52*, 8629. (i) Li, Y.; Chakrabarty, S.; Mück-Lichtenfeld, C.; Studer, A. Ortho-Trialkylstannyl Arylphosphanes by C-P and C-Sn Bond Formation in Arynes. *Angew. Chem., Int. Ed.* **2016**, *55*, 802. (j) Ahire, M. M.; Khan, R.; Mhaske, S. B. Synthesis of *o*-Methyl Trifluoromethyl Sulfide Substituted Benzophenones via 1,2-Difunctionalization of Aryne by Insertion into the C–C Bond. *Org. Lett.* **2017**, *19*, 2134.

(6) For selected recent reports on multicomponent reactions involving arynes, see: (a) Yoshioka, E.; Kohtani, S.; Miyabe, H. A Multicomponent Coupling Reaction Induced by Insertion of Arynes into the C = O Bond of Formamide. *Angew. Chem., Int. Ed.* **2011**, *50*, 6638. (b) Allan, K. M.; Gilmore, C. D.; Stoltz, B. M. Benzannulated Bicycles by Three-Component Aryne Reactions. *Angew. Chem., Int. Ed.* **2011**, *50*, 4488. (c) Bhunia, A.; Roy, T.; Pachfule, P.; Rajamohanan, P. R.; Biju, A. T. Transition-Metal-Free Multicomponent Reactions Involving Arynes, N-Heterocycles, and Isatins. *Angew. Chem., Int. Ed.* **2013**, *52*, 10040. (d) Nawaz, F.; Mohanan, K.; Charles, L.; Rajzmann, M.; Bonne, D.; Chuzel, O.; Rodriguez, J.; Coquerel, Y. Temporary Intramolecular Generation of Pyridine Carbenes in Metal-Free Three-Component C-H Bond Functionalisation/Aryl-Transfer Reactions. *Chem. - Eur. J.* **2013**, *19*, 17578. (e) Bhojgude, S. S.; Baviskar, D. R.; Gonnade, R. G.; Biju, A. T. Three-Component Coupling Involving Arynes, Aromatic Tertiary Amines, and Aldehydes via Aryl–Aryl Amino Group Migration. *Org. Lett.* **2015**, *17*, 6270.

(7) (a) Tadross, P. M.; Stoltz, B. M. A Comprehensive History of Arynes in Natural Product Total Synthesis. *Chem. Rev.* **2012**, *112*, 3550. Also see references cited therein. (b) Vaidya, S. D.; Argade, N. P. Aryne Insertion Reactions Leading to Bioactive Fused Quinazolinones: Diastereoselective Total Synthesis of Cruciferane. *Org. Lett.* **2013**, *15*, 4006. (c) Styduhar, E. D.; Huters, A. D.; Weires, N. A.; Garg, N. K. Enantiospecific Total Synthesis of N-Methylwelwitindolinone D Isonitrile. *Angew. Chem., Int. Ed.* **2013**, *52*, 12422. (d) Gouthami, P.; Chegondi, R.; Chandrasekhar, S. Formal Total Synthesis of (±)-Cephalotaxine and Congeners via Aryne Insertion Reaction. *Org. Lett.* **2016**, *18*, 2044. (e) Yao, T.; Zhang, H.; Zhao, Y. Synthesis of 9,10-Phenanthrenes via Palladium-Catalyzed Aryne

DOI: 10.1021/acs.joc.9b00488
J. Org. Chem. 2019, 84, 5957–5964

Annulation by o-Halostyrenes and Formal Synthesis of (±)-Tylophorine. *Org. Lett.* **2016**, *18*, 2532. (f) Samineni, R.; Srihari, P.; Mehta, G. Versatile Route to Benzoannulated Medium-Ring Carbocycles via Aryne Insertion into Cyclic 1,3-Diketones: Application to a Synthesis of Radermachol. *Org. Lett.* **2016**, *18*, 2832.

(8) (a) Dhokale, R. A.; Thakare, P. R.; Mhaske, S. B. Transition-Metal-Free C-Arylation at Room Temperature by Arynes. *Org. Lett.* **2012**, *14*, 3994. (b) Mohanan, K.; Coquerel, Y.; Rodriguez. Transition-Metal-Free α-Arylation of β-Keto Amides via an Interrupted Insertion Reaction of Arynes. *Org. Lett.* **2012**, *14*, 4686.

(9) Gupta, E.; Kant, R.; Mohanan, K. Decarbethoxylative Arylation Employing Arynes: A Metal-Free Pathway to Arylfluoroamides. *Org. Lett.* **2017**, *19*, 6016.

(10) (a) Kupchan, S. M.; Sigel, C. W.; Matz, M. J.; Gilmore, C. J.; Bryan, R. F. Structure and Stereochemistry of Jatrophone, a Novel Macrocyclic Diterpenoid Tumor Inhibitor. *J. Am. Chem. Soc.* **1976**, *98*, 2295. (b) Saimoto, H.; Hiyama, T.; Nozaki, H. Regiocontrolled Hydration of 2-Butyne-1,4-Diol Derivatives to give 4,5-Dihydro-3(2H)-Furanones. Practical Synthesis of Bullatenone and Geiparvarin. *J. Am. Chem. Soc.* **1981**, *103*, 4975. (c) Smith, A. B., III; Guaciaro, M. A.; Schow, S. R.; Wovkulich, P. M.; Toder, B. H.; Hall, T. W. A Strategy for the Total Synthesis of Jatrophone: Synthesis of Normethyljatrophone. *J. Am. Chem. Soc.* **1981**, *103*, 219. (d) Curran, D. P.; Singleton, D. H. Reduction of Δ^2-Isoxazolines-2. A Facile Synthesis of 3(2H)-Furanones. *Tetrahedron Lett.* **1983**, *24*, 2079. (e) Wolff, S.; Agosta, W. C. 3(2H)-Furanones From Mercuric Acetate Oxidation of Allenic Ketones. A Synthesis of Bullatenone. *Tetrahedron Lett.* **1985**, *26*, 703.

(11) (a) Jackson, R. F. W.; Raphael, R. A. New Syntheses of Bullatenone and Geiparvarin. *Tetrahedron Lett.* **1983**, *24*, 2117. (b) Mack, R. A.; Zazulak, W. I.; Radov, L. A.; Baer, J. E.; Stewart, J. D.; Elzer, P. H.; Kinsolving, C. R.; Georgiev, V. S. Drug-Induced Modifications of the Immune Response. 12. 4,5-Dihydro-4-Oxo-2-(Substituted Amino)-3-Furancarboxylic Acids and Derivatives as Novel Antiallergic Agents. *J. Med. Chem.* **1988**, *31*, 1910. (c) Felman, S. W.; Jirkovsky, I.; Memoli, K. A.; Borella, L.; Wells, C.; Russell, J.; Ward, J. Synthesis and Antiulcer Activity of Novel 5-(2-Ethenyl substituted)-3(2H)-Furanones. *J. Med. Chem.* **1992**, *35*, 1183. (d) Villemin, D.; Jaffrès, P.-A.; Hachémi, M. An Abnormal Reaction of Esters of 3-Hydroxy-3-methylbutan-2-one. A Rapid Synthesis of Bullatenone and Geiparvarin. *Tetrahedron Lett.* **1997**, *38*, 537. (e) Sakamoto, H. T.; Flausino, D.; Castellano, E. E.; Stark, C. B. W.; Gates, P. J.; Lopes, N. P. Sesquiterpene Lactones from Lychnophora ericoides. *J. Nat. Prod.* **2003**, *66*, 693. (f) Shin, S. S.; Byun, Y.; Lim, K. M.; Choi, J. K.; Lee, K.-W.; Moh, J. H.; Kim, J. K.; Jeong, Y. S.; Kim, J. Y.; Choi, Y. H.; Koh, H.-J.; Park, Y.-H.; Oh, Y. I.; Noh, M.-S.; Chung, S. In Vitro Structure−Activity Relationship and in Vivo Studies for a Novel Class of Cyclooxygenase-2 Inhibitors: 5-Aryl-2,2-dialkyl-4-phenyl-3(2*H*)furanone Derivatives. *J. Med. Chem.* **2004**, *47*, 792.

(12) (a) Henry, D. W.; Silverstein, R. M. A Rational Synthesis of 4-Hydroxy-2,5-dimethyl-3(2H)-furanone, a Flavor Component of Pineapple. *J. Org. Chem.* **1966**, *31*, 2391. (b) Jerris, P. J.; Smith, A. B., III. Synthesis and Configurational Assignment of Geiparvarin: A Novel Antitumor Agent. *J. Org. Chem.* **1981**, *46*, 577. (c) Antonioletti, R.; Bonadies, F.; Prencipe, T.; Scettri, A. Furan-3(2*H*)-ones by Tandem Photo-Oxidation−Intramolecular Michael Addition. *J. Chem. Soc., Chem. Commun.* **1988**, 850. (d) Winkler, J. D.; Oh, K.; Asselin, S. M. Synthesis of Highly Functionalized Furanones via Aldol Reaction of 3-Silyloxyfurans. *Org. Lett.* **2005**, *7*, 387. (e) Poonoth, M.; Krause, N. Cycloisomerization of Bifunctionalized Allenes: Synthesis of 3(2H)-Furanones in Water. *J. Org. Chem.* **2011**, *76*, 1934. (f) Liu, Y.; Liu, M.; Guo, S.; Tu, H.; Zhou, Y.; Gao, H. Gold-Catalyzed Highly Efficient Access to 3(2*H*)-Furanones from 2-Oxo-3-butynoates and Related Compounds. *Org. Lett.* **2006**, *8*, 3445. (g) Kirsch, S. F.; Binder, J. T.; Liébert, C.; Menz, H. Gold(III)- and Platinum(II)-Catalyzed Domino Reaction Consisting of Heterocyclization and 1,2-Migration: Efficient Synthesis of Highly Substituted 3(2H)-Furanones. *Angew. Chem., Int. Ed.* **2006**, *45*, 5878. (h) Silva, F.; Reiter, M.; Mills-Webb, R.; Sawicki, M.; Klär, D.; Bensel, N.; Wagner, A.; Gouverneur, V. Pd(II)-Catalyzed Cascade Wacker-Heck Reaction: Chemoselective Coupling of Two Electron-Deficient Reactants. *J. Org. Chem.* **2006**, *71*, 8390. (i) Marson, C. M.; Edaan, E.; Morrell, J. M.; Coles, S. J.; Hursthouse, M. B.; Davies, D. T. A Catalytic Asymmetric Protocol for the Enantioselective Synthesis of 3(2H)-Furanones. *Chem. Commun.* **2007**, 2494. (j) Dou, X.; Han, X.; Lu, Y. From the Feist−Bénary Reaction to Organocatalytic Domino Michael−Alkylation Reactions: Asymmetric Synthesis of 3(2 H)-Furanones. *Chem. - Eur. J.* **2012**, *18*, 85. (k) Yan, Y.-Y.; Lu, R.-J.; Wang, J.-J.; Xuan, Y.-N.; Yan, M. Synthesis of Chiral Tetronic Acid Derivatives via Organocatalytic Conjugate Addition of Ethyl 4-Chloro-3-Oxobutanoate to Nitroalkenes. *Tetrahedron* **2012**, *68*, 6123.

(13) (a) John, J.; Hopf, H. Substituted 3(2*H*)-Furanones by a Tandem Michael Addition/Palladium Catalyzed Ring-Closing Protocol. *Eur. J. Org. Chem.* **2013**, *2013*, 841. (b) John, J.; Târcoveanu, E.; Jones, P. G.; Hopf, H. A Tandem Mannich Addition-Palladium Catalyzed Ring-Closing Route Toward 4-Substituted-3(2H)-Furanones. *Beilstein J. Org. Chem.* **2014**, *10*, 1462.

(14) See the Supporting Information.

(15) Pashkovskii, F. S.; Shchukina, E. M.; Gribovskii, M. G.; Lakhvich, F. A. Heterocyclic Analogs of Prostaglandins: III. Synthesis of 10-Oxa-13-Aza, 11-Oxa-13-Aza, and 9-Oxa-7-Aza Prostanoids from 3-Acyl-and 3-(3-Arylprop-2-enoyl)Furan-2,4-Diones. *Russ. J. Org. Chem.* **2006**, *42*, 527. See also references cited therein.

(16) Choi, H. Y.; Chi, D. Y. Nonselective Bromination−Selective Debromination Strategy: Selective Bromination of Unsymmetrical Ketones on Singly Activated Carbon against Doubly Activated Carbon. *Org. Lett.* **2003**, *5*, 411.

DOI: 10.1021/acs.joc.9b00488
J. Org. Chem. 2019, 84, 5957−5964