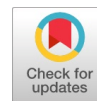


# Advancements in Inverse-Electron-Demand Diels–Alder Cycloaddition of 2-Pyrones: Mechanisms, Methodologies



Nasser Thallaj

**Abstract:** The Diels–Alder (DA) cycloaddition is well-known for its effectiveness in synthesizing natural products and multifunctional materials. This article explicitly explores the inverse-electron-demand Diels–Alder (IEDDA) cycloaddition involving 2-pyrones, which exhibit ambiphilic properties due to their unique electronic characteristics. We investigate the mechanisms underlying IEDDA, with a focus on how electron-donating and electron-withdrawing substituents influence reactivity and product selectivity. Various methodologies are reviewed, encompassing non-catalytic and catalytic approaches. Special attention is given to advancements in microwave-assisted techniques and high-pressure conditions, which enhance both reaction efficiency and selectivity. Additionally, the synthesis of chiral bridged bicyclic lactones from substituted 2-pyrones is examined, illustrating their versatility in organic synthesis. This review highlights the importance of IEDDA cycloaddition in developing innovative synthetic routes for constructing complex molecular structures.

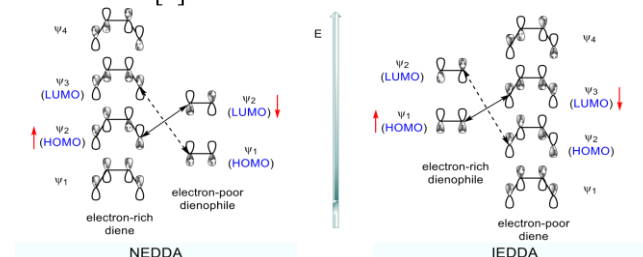
**Keywords:** Diels–Alder Cycloaddition; Inverse-Electron-Demand; 2-Pyrones; Electrophilic Dienes; Microwave-Assisted Synthesis; Chiral Bicyclic Lactones; Reaction Mechanisms.

## I. INTRODUCTION

Over the past century, the Diels–Alder (DA) cycloaddition has proven its significance in synthesizing natural products and multifunctional materials since its discovery by Otto Diels and Kurt Alder in 1928 [1]. The method's effectiveness lies in its ability to form six-membered rings with four adjacent stereocenters in a single reaction step, coupled with its favorable regio- and stereoselectivity. These attributes have prompted chemists to investigate the molecular mechanisms underlying DA cycloaddition, enabling them to predict new reactions better.

The Frontier Molecular Orbital (FMO) theory provides a foundational model for understanding HOMO/LUMO interactions and categorizes DA cycloadditions into two types. The first is the normal-electron-demand Diels–Alder (NEDDA) cycloaddition, involving the [4+2] cycloaddition of electron-rich dienes with electron-poor dienophiles.

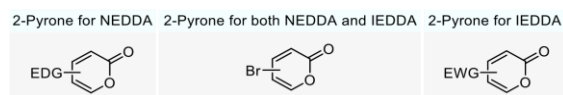
The second type, the inverse-electron-demand Diels–Alder (IEDDA) cycloaddition, utilizes [4+2] cycloadditions with electron-poor dienes and electron-rich dienophiles. Typically, an electron-donating group elevates the HOMO level, whereas an electron-withdrawing group lowers the LUMO level [2].



**Scheme 1. Difference Between NEDDA and IEDDA Cycloadditions in H Molecular Orbitals**

Despite its aromatic nature, 2-pyrone can be considered as a 1,3-butadiene with an electron-withdrawing carboxyl group at one end and an electron-donating acyloxy group at the other. This structure enables 2-pyrone to react with both electron-rich and electron-poor dienophiles, thereby conferring ambiphilic properties. However, unsubstituted 2-pyrone often undergoes self-polymerization challenges under thermal conditions. In contrast, substituted 2-pyrones are effective in Diels–Alder (DA) cycloadditions, where the electronic properties of the substituents dictate the reaction type.

Electron-rich 2-pyrones are known to serve as good dienes for normal-electron-demand Diels–Alder (NEDDA) cycloadditions. On the other hand, electron-poor 2-pyrones can act as electrophilic dienes in an inverse-electron-demand manner, exhibiting higher reactivity due to the electron-withdrawing group disrupting internal electron delocalization (thus reducing aromaticity) and lowering the LUMO level. Notably, bromo- and dibromo-substituted 2-pyrones demonstrate flexible participation in both NEDDA and inverse-electron-demand cycloadditions [3].



**Scheme 2. Ambiphilic Capacity of 2-Pyrones**

In recent decades, significant attention has focused on developing inverse-electron-demand Diels–Alder (IEDDA) cycloadditions and their synthetic applications.

Manuscript received on 13 September 2024 | Revised Manuscript received on 27 September 2024 | Manuscript Accepted on 15 October 2024 | Manuscript published on 30 October 2024.

\* Correspondence Author (s)

**Prof. Dr. Nasser Thallaj\***, Pharmaceutical Chemistry and Drug Quality Control Department, Faculty of Pharmacy, Al-Rachid Private University, Damascus (Syria), West Asia. Email ID: [proftallaj@gmail.com](mailto:proftallaj@gmail.com) ORCID ID: [0000-0002-6279-768X](https://orcid.org/0000-0002-6279-768X)

© The Authors. Published by Lattice Science Publication (LSP). This is an open-access article under the CC-BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

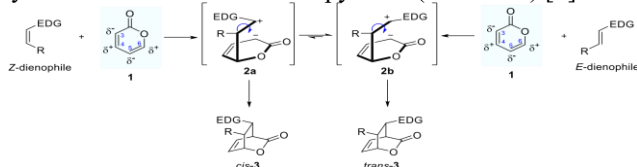
Among these, derivatives of 2-pyrone have attracted interest due to their ability to synthesize bridged bicyclic lactones and derivatives, including densely functionalized 1,3-cyclohexadienes through CO<sub>2</sub> extrusion and polysubstituted aromatic compounds via release of small molecules. Initially, many non-catalytic IEDDA cycloadditions were established, typically facilitated by direct heating or high pressure. Despite their efficiency, these reactions produced racemic mixtures of bridged bicyclic lactones, limiting their usefulness in total synthesis. In contrast, catalytic IEDDA cycloadditions using Lewis acids and organocatalysts have garnered considerable interest over the past three decades. These catalytic methods enable the efficient formation of various chiral bridged bicyclic lactones that are inaccessible through non-catalytic means.

This discussion begins with a brief overview of the mechanism of IEDDA cycloaddition involving electrophilic 2-pyrones, followed by a detailed examination of non-catalytic, Lewis acid-catalyzed, and organocatalytic IEDDA cycloadditions with activated alkenes in subsequent sections [3].

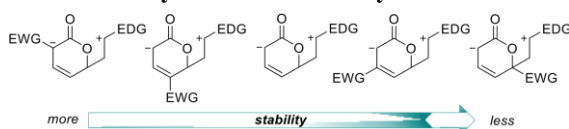
## II. MECHANISM

The electron density distribution of 2-pyrone and its derivatives, depicted in Scheme 3, reveals high electron density at the C3 and C5 positions, while the C4 and C6 positions exhibit electron deficiency. Consequently, the C6 position of 2-pyrone is electrophilic, and the C3 position is nucleophilic, making it an excellent diene for IEDDA cycloaddition [4].

It is well established that the Diels–Alder (DA) cycloaddition involving highly polarized derivatives of 2-pyrone and dienophiles proceeds stepwise rather than through a conventional concerted mechanism, as shown in Scheme 5. When a Z or E dienophile reacts with 2-pyrone under thermal or catalytic conditions, trans-3 is typically the major product. This outcome is rationalized by the formation of intermediate 2, where for a Z dienophile, rotation occurs from conformer 2a to the more stable conformer 2b, leading to the final product trans-3. From an electron density perspective, electron-withdrawing groups on the pyrone ring can accelerate the rate of IEDDA cycloaddition. Moreover, intermediates derived from 3-substituted and 5-substituted 2-pyrones are notably more stable than those from 4-substituted and 6-substituted variants, which aligns with resonance stabilization and supports the results observed in the IEDDA cycloaddition of substituted 2-pyrones (Scheme 4) [5].



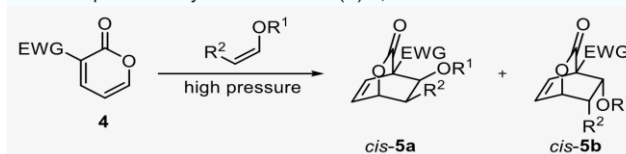
**Scheme 3. Stepwise Mechanism of the IEDDA Cycloaddition of 2-Pyrone**



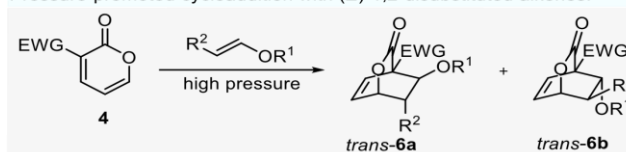
**Scheme 4. Comparison of the Stability of Different Reaction Intermediates**

Conversely, Posner and Cho observed that the IEDDA cycloaddition of 3-substituted 2-pyrones, when conducted under high pressure, proceeded in a concerted manner. They discovered that cis products five were exclusively formed from the cycloaddition of 3-substituted 2-pyrones 4 with (Z)-1,2-disubstituted alkenes, whereas trans products 6 resulted from the reaction of 3-substituted 2-pyrones 4 with (E)-1,2-disubstituted alkenes under high-pressure conditions (Scheme 5) [6].

Pressure-promoted cycloaddition with (Z)-1,2-disubstituted alkenes:



Pressure-promoted cycloaddition with (E)-1,2-disubstituted alkenes:

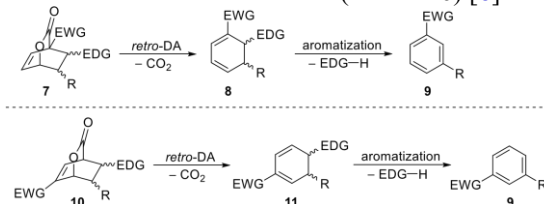


**Scheme 5. Stereospecificity of the Pressure-Promoted IEDDA Cycloaddition**

### Non-Catalytic IEDDA Cycloaddition

Over the past 50 years, extensive research has been conducted on the non-catalytic IEDDA cycloaddition of electrophilic 2-pyrones, focusing primarily on dienes such as carbonyl-substituted, bromosubstituted, and sulfur-substituted 2-pyrones. Common dienophiles employed in these reactions include ketene acetals, enamines, and vinyl ethers. The IEDDA cycloaddition can be facilitated through direct heating or high pressure [7].

It is noteworthy that the initially formed bridged bicyclic products are unstable at elevated temperatures, leading to CO<sub>2</sub> extrusion via a retro-DA cycloaddition. This process yields highly functionalized cyclohexadienes, which can subsequently transform various substituted arenes through the elimination of a small molecule (Scheme 6) [8].



**Scheme 6. Conversion of Bridged Bicyclic Lactones Under Thermal Conditions**

In recent years, significant advancements have been made due to the emergence of microwave technology and the introduction of new dienophiles, which will be discussed in this section.

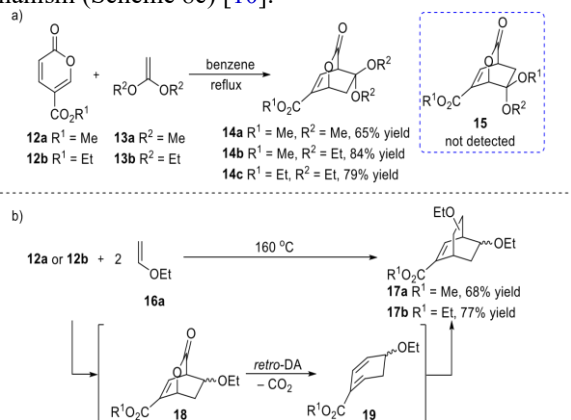
### IEDDA Cycloaddition of Carbonyl-Substituted 2-Pyrones

As previously noted, 3-substituted and 5-substituted 2-pyrones exhibit higher reactivity in IEDDA cycloadditions compared to their 4-substituted and 6-substituted counterparts, owing to the resonance stabilization of reaction intermediates.

The following subsections will explore different classes of 2-pyrones containing a carbonyl group at various positions [9].

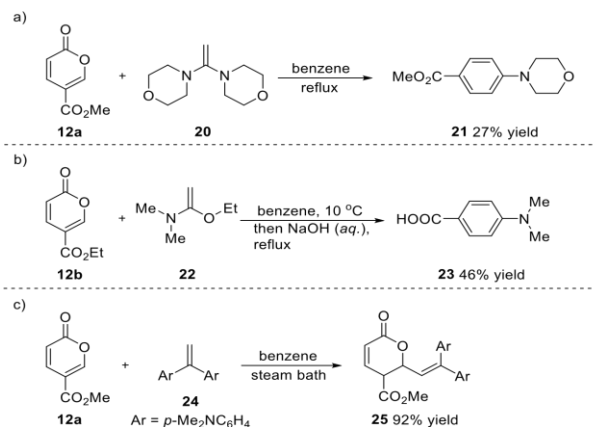
### IEDDA Cycloaddition of 5-Carbonyl-2-Pyrones

The first reported instance of IEDDA cycloaddition involving 2-pyrones dates back to 1969, where alkyl coumalates 12 reacted with various electron-rich dienophiles. When 1,1-dialkoxyethenes 13 were employed as dienophiles, the reaction yielded exclusively bridged bicyclic compounds 14 in good yields, without detection of regioisomer 15 (Scheme 7a). A similar outcome was observed with 2-pyrones 12 and ethyl vinyl ether 16a; however, the resulting cycloadducts 18 proved thermally unstable at 160 °C, undergoing retro-DA cycloaddition to produce cyclohexadienes 19. These cyclohexadienes further underwent additional cycloaddition with another equivalent of ethyl vinyl ether 16a, yielding 1:2-adducts 17. Due to limitations in high-resolution NMR technology, the precise position of the second ethoxy group in adducts 17 could not be determined by the authors (Scheme 7b). Attempts to explore other substrates did not yield the expected bicyclic adducts. For example, reactions of 1,1-dimorpholinoethylene 20 and 1-dimethylamino-1-ethoxyethylene 22 with 2-pyrones resulted in the corresponding aromatic compounds 21 and 23 (Schemes 8a and 8b). Furthermore, increasing the electron density and steric hindrance of the pyrone ring facilitated the conversion of bridged bicyclic adducts into aromatic compounds. Notably, boiling a mixture of methyl coumalate 12a and N,N-dimethyl-4-vinylaniline 24 in benzene produced adduct 25, providing evidence supporting a stepwise mechanism (Scheme 8c) [10].



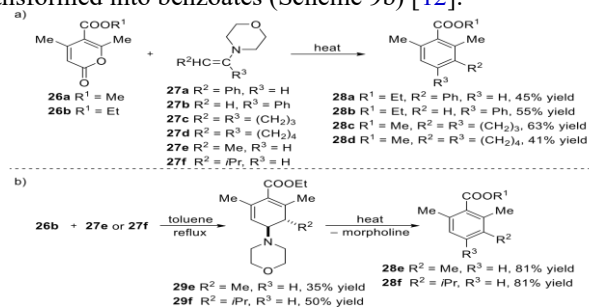
**Scheme 7. Thermal IEDDA Cycloaddition of Alkyl Coumalates with Alkoxyethenes**

The precise position of the second ethoxy group in adducts 17 could not be determined due to limitations in high-resolution NMR technology (Scheme 7b). Explorations with other substrates did not yield the expected bicyclic adducts. For example, reactions of 1,1-dimorpholinoethylene 20 and 1-dimethylamino-1-ethoxyethylene 22 with 2-pyrones resulted in aromatic compounds 21 and 23, as depicted in Schemes 8a and 8b [11]. Additionally, increasing the electron density and steric hindrance of the pyrone ring facilitated the conversion of bridged bicyclic adducts into aromatic compounds. Notably, boiling a mixture of methyl coumalate 12a and N,N-dimethyl-4-vinylaniline 24 in benzene produced adduct 25, providing supportive evidence for a stepwise mechanism (Scheme 8c).



**Scheme 8. Thermal IEDDA Cycloaddition of Alkyl Coumalates with Substituted Alkenes**

In 1983, the excellent leaving ability of morpholine was observed during the study of the regioselectivity in the IEDDA cycloaddition between 2-pyrones and morpholine enamines. Under thermal conditions, 2-pyrones 26 reacted with substituted morpholine enamines 27, initiating an IEDDA cycloaddition followed by CO<sub>2</sub> extrusion through a retro-DA cycloaddition. This sequence led to the aromatization via elimination of morpholine, resulting in a series of highly functionalized benzoates 28 with complete regioselectivity (Scheme 9a). In two instances, cyclohexadiene intermediates 29 were isolated and characterized, and upon thermolysis, they were further transformed into benzoates (Scheme 9b) [12].

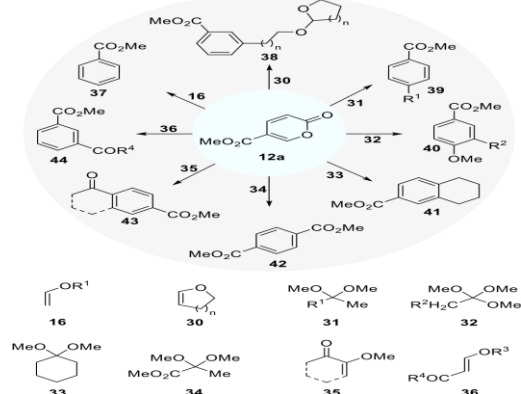


**Scheme 9. Thermal IEDDA Cycloaddition of 2-Pyrones with Morpholine Enamines**

The cycloaddition of 2-pyrones offers a sustainable approach to accessing highly functionalized aromatic compounds, thereby reducing reliance on dwindling petroleum sources. Methyl coumalate, for example, can be easily produced by dimerizing malic acid, derived from glucose fermentation. Various dienophiles have been tested for their reaction with methyl coumalate 12a to form substituted benzoates, as well as for milder conditions to convert malic acid into coumalic acid. Several vinyl ethers, ketals, and orthoesters were evaluated, as depicted in Scheme 10. In 2013, researchers investigated the cycloaddition of methyl coumalate 12a with vinyl ethers (16, 30, 35, 36) and masked vinyl ethers, such as ketals (31, 33) and orthoesters (32), under thermal conditions. This transformation occurred in a domino sequence involving IEDDA cycloaddition, CO<sub>2</sub> evolution, and alcohol elimination, resulting in a diverse array of aromatic compounds [13].



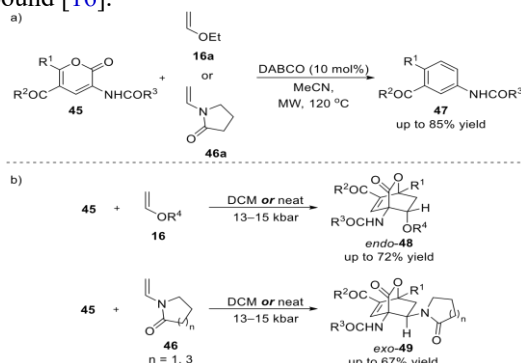
In the plastics industry, dimethyl terephthalate (DMT, 42) is extensively used for large-scale production of bis(2-hydroxyethyl) terephthalate (BHET), a crucial monomer for polyethylene terephthalate (PET), the most widely used thermoplastic polymer. In 2014, a renewable method for synthesizing DMT was reported, involving the IEDDA cycloaddition of methyl coumalate 12a with captodative ketal 34. This approach provides an alternative to reduce dependence on petroleum products [14].



**Scheme 10. Thermal IEDDA Cycloaddition of Methyl Coumalate with Vinyl Ethers, Ketals, and Orthoesters**

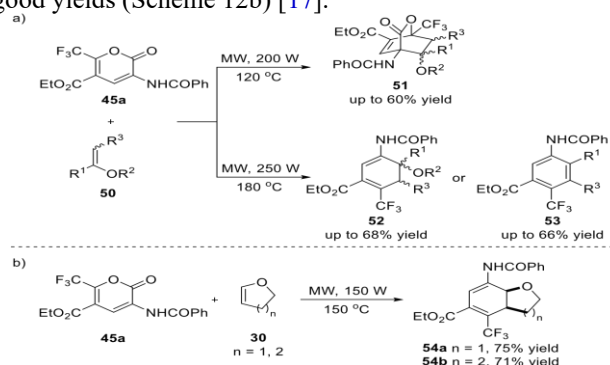
Conventional thermal conditions for the IEDDA cycloaddition to produce aromatic compounds typically require either high temperatures (up to 220 °C) or extended reaction times (up to 10 days). Microwave irradiation offers a solution to these limitations. A microwave-assisted IEDDA cycloaddition involving 2-pyrone derivatives 45 with ethyl vinyl ether 16a and enamine 46a has been reported, rapidly yielding substituted anilines 47 (Scheme 11a). In this transformation, a catalytic amount of DABCO was crucial. Control experiments demonstrated that DABCO facilitated the aromatization step rather than the cycloaddition or CO<sub>2</sub> extrusion [15].

Bicyclic adducts endo-48 and exo-49 were synthesized through the cycloaddition of 2-pyrone derivatives 45 with vinyl ethers 16 and enamines 46 under high pressure, with no significant difference observed whether DABCO was included or not (Scheme 11b), suggesting that DABCO did not affect the cycloaddition step. Furthermore, when the resulting bridged bicyclic lactone was subjected to microwave irradiation without DABCO, a mixture of cyclohexadiene and aromatic compound was obtained in a 7:1 ratio. In contrast, the presence of DABCO under the same reaction conditions led to the complete conversion of the bridged bicyclic lactone into the corresponding aromatic compound [16].



**Scheme 11. Comparison of Microwave-Assisted and High Pressure-Promoted IEDDA Cycloadditions of 2-Pyrones**

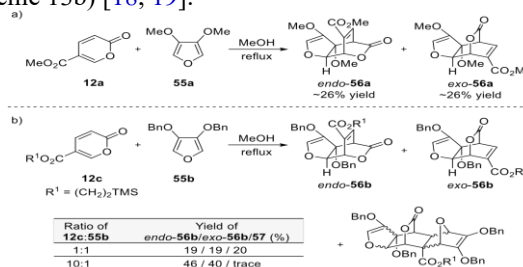
Motivated by the importance of the trifluoromethyl group in bioactive compounds, researchers developed a microwave-assisted IEDDA cycloaddition of 5-carboethoxy-2-pyrone 45a, featuring a trifluoromethyl group at the C6 position, with acyclic vinyl ethers 50. By optimizing the reaction conditions, they rapidly obtained bridged bicyclic adducts 51, cyclohexadienes 52, and aromatic compounds 53 (Scheme 12a). Subsequently, the authors expanded the substrate scope to include cyclic vinyl ethers 30. These cyclic vinyl ethers underwent IEDDA cycloaddition with 45a, resulting in substituted dihydrobenzofuran 54a and chromane 54b in good yields (Scheme 12b) [17].



**Scheme 12. Microwave-Assisted IEDDA Cycloaddition Of 2-Pyrone with Acyclic and Cyclic Vinyl Ethers**

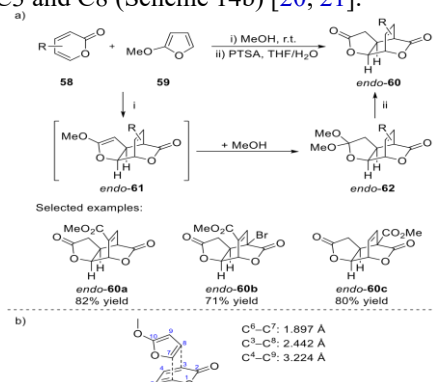
Electron-rich heteroarenes, such as furans and indoles, which feature a masked O-substituted or N-substituted alkene, serve as effective dienophiles for IEDDA cycloaddition with 2-pyrones, despite the stability conferred by their aromatic nature. In 1986, it was discovered that alkyl coumalates 12 engage in a [4+2] cycloaddition with 3,4-dialkoxyfurans 55 in an inverse-electron-demand manner. In this reaction, alkyl coumalates 12 act as the electrophilic dienes, while the dialkoxyethene moiety of 3,4-dialkoxyfurans 55 functions as the dienophile, yielding bridged lactones 56 with high regioselectivity (Scheme 13).

For example, the IEDDA cycloaddition between methyl coumalate 12a and 3,4-dimethoxyfuran 55a was carried out in boiling methanol for 2 hours, resulting in cycloadducts 56a as a 1:1 mixture of endo and exo isomers (Scheme 13a). Furthermore, the formation of cycloadduct 57, derived from a second Diels–Alder reaction of 56b, was observed when equimolar amounts of analogous components 12c and 55b were used. This issue was resolved by adjusting the ratio of starting materials 12c and 55b to 10:1, leading to the detection of only a trace amount of the over-addition product 57 (Scheme 13b) [18, 19].



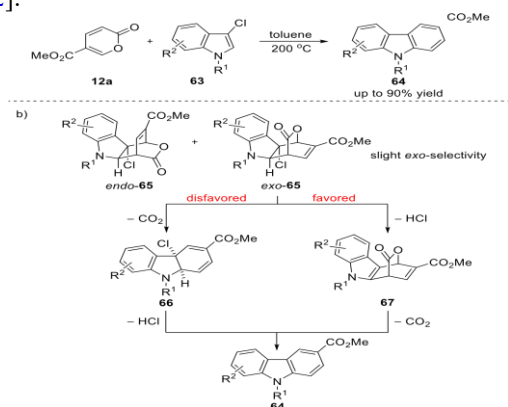
**Scheme 13. Thermal IEDDA Cycloaddition of Alkyl Coumalates With 3,4-Dialkoxyfurans**

In 2000, a similar reaction was reported where 2-methoxyfuran 59 acted as the dienophile (Scheme 14). Stirring a mixture of 2-pyrones 58 and 2-methoxyfuran 59 in methanol resulted in the formation of bridged lactones endo-61, which proved unstable during purification via column chromatography. The addition of methanol to the transiently formed ketals endo-61 produced orthoesters endo-62, which, upon hydrolysis with *p*-toluenesulfonic acid, transformed into the corresponding dilactones endo-60 (Scheme 14a). Semiempirical calculations (AM1 and PM3) provided substantial evidence supporting both the inverse-electron-demand pathway and the stepwise mechanism, indicating that the calculated distance between C6 and C7 is shorter than that between C3 and C8 (Scheme 14b) [20, 21].



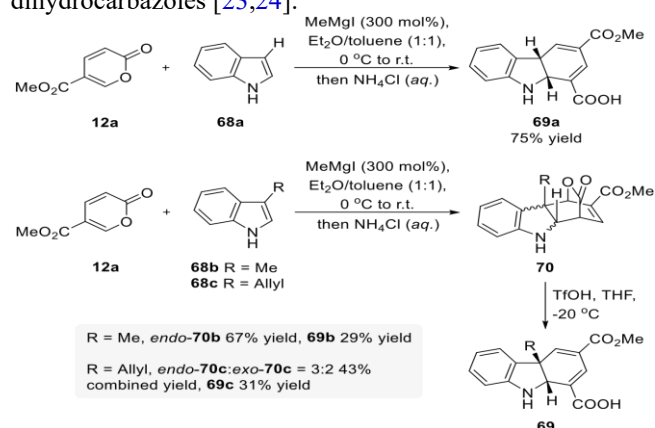
**Scheme 14. IEDDA Cycloaddition Of 2-Pyrones With 2-Methoxyfuran**

Indoles substituted with group 63 were initially studied as dienophiles in the IEDDA cycloaddition with methyl coumalate 12a to produce highly functionalized carbazoles 64 in 2014 (Scheme 15a). This process involved a cascade sequence including IEDDA cycloaddition, CO<sub>2</sub> extrusion, and HCl elimination. To address the aromaticity of indoles, a chloride, a good leaving group, was introduced at the C3 position. Although the IEDDA cycloaddition step is both kinetically and thermodynamically unfavorable, the simultaneous elimination of HCl and CO<sub>2</sub> makes this step irreversible. Furthermore, the alkyl protecting group on the nitrogen atom significantly decreased the decomposition of indoles under harsh conditions (up to 200 °C). In 2015, DFT calculations were used to elucidate the potential pathway for this reaction. These calculations showed that the IEDDA cycloaddition proceeded with slight *exo* stereoselectivity, and that the initial HCl elimination during the aromatization step was kinetically favored over CO<sub>2</sub> extrusion (Scheme 15b) [21,22].



**Scheme 15. Thermal IEDDA Cycloaddition of Methyl Coumalate With 1-Alkyl-3-Chloroindoles**

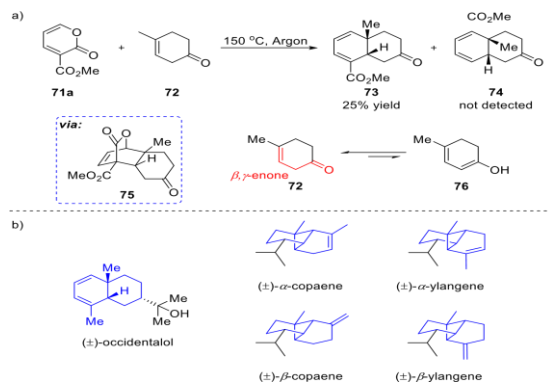
Recently, it was discovered that indolemagnesium iodides, formed in situ from unprotected indoles 68 using methylmagnesium iodide, reacted with methyl coumalate 12a to produce dihydrocarbazoles 69 via an inverse-electron-demand process (Scheme 16). When 3-alkylindoles 68b and 68c were used as dienophiles, bridged lactones 70 were isolated and characterized. However, both underwent retro-DA cycloaddition at room temperature, reverting to the starting materials. Further treatment with trifluoromethanesulfonic acid converted bridged lactones 70 into dihydrocarbazoles 69 through a lactone-opening reaction. Unfortunately, this reaction exhibited a limited substrate scope and resulted in low yields of dihydrocarbazoles [23,24].



**Scheme 16. IEDDA Cycloaddition of Methyl Coumalate with Nonprotected Indoles**

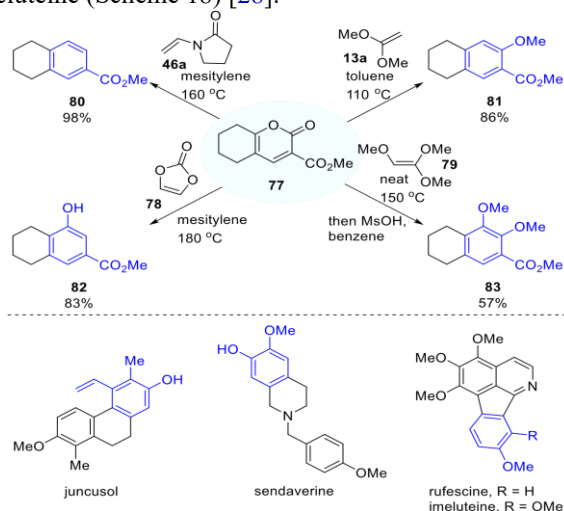
### IEDDA Cycloaddition of 3-Carbonyl-2-Pyrones

3-Carbomethoxy-2-pyrone has drawn considerable interest among synthetic chemists, although it has been studied less extensively compared to 5-carbomethoxy-2-pyrone. This compound, 3-carbomethoxy-2-pyrone 71a, can be easily synthesized via a Knoevenagel condensation reaction between a malonate derivative and 1,1,3,3-tetramethoxypropane, followed by acid-mediated cyclization. In 1972, a novel synthetic approach was developed involving a thermal IEDDA cycloaddition of 3-carbomethoxy-2-pyrone 71a with 4-methyl-3-cyclohexenone 72, acting as a masked dienophile, to produce *cis*-fused bicyclo[4.4.0]decane 73 with complete regio- and stereocontrol. The regioisomer 74 was absent in the resulting mixture. Other similar dienophiles, such as 4-substituted-1-methylcyclohexenes lacking a  $\beta,\gamma$ -enone moiety, did not undergo the IEDDA cycloaddition with 3-carbomethoxy-2-pyrone under the same conditions, indicating that the reactive species in this reaction is the electron-rich dienol 76, formed in situ from  $\beta,\gamma$ -enone 72 through enolization. The synthetic utility of this transformation was demonstrated through the total synthesis of several sesquiterpenes, including ( $\pm$ )-occidentalol, ( $\pm$ )- $\alpha$ -copaene, ( $\pm$ )- $\alpha$ -ylangene, ( $\pm$ )- $\beta$ -copaene, and ( $\pm$ )- $\beta$ -ylangene (Scheme 17) [24-27].



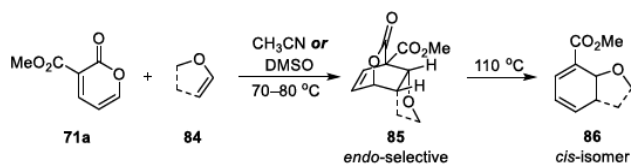
**Scheme 17. Thermal IEDDA Cycloaddition Of 3-Carbomethoxy-2-Pyrone With 4-Methyl-3-Cyclohexenone**

In the presence of a suitable leaving group on the dienophile, the domino sequence of IEDDA cycloaddition, CO<sub>2</sub> extrusion, and aromatization can generate substituted aromatic compounds. This concept was further explored using 3-carbomethoxy-2-pyrone. Researchers discovered that the derivative 77 of 3-carbomethoxy-2-pyrone could undergo IEDDA cycloaddition with N-vinyl-2-pyrrolidinone 46a, 1,1-dimethoxyethene 13a, vinylene carbonate 78, and 1,1,2-trimethoxyethene 79, followed by CO<sub>2</sub> extrusion and aromatization to yield aromatic compounds 80–83. The synthetic utility of these methods was demonstrated through the total synthesis of juncusol, sendaverine, rufescine, and imeluteine (Scheme 18) [28].

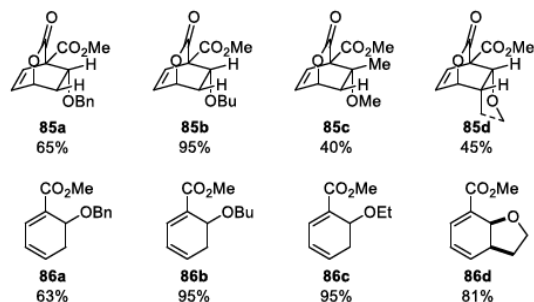


**Scheme 18. The IEDDA Cycloaddition/CO<sub>2</sub> Extrusion/Aromatization Sequence Of 2-Pyrone Derivative with Various Dienophiles**

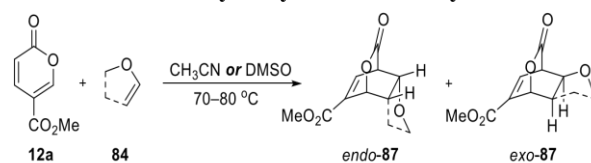
In 1993, an intriguing comparison was drawn between 3-carbomethoxy-2-pyrone and 5-carbomethoxy-2-pyrone in the context of IEDDA cycloaddition. Their thermal IEDDA cycloaddition with various vinyl ethers 84 proceeded efficiently at atmospheric pressure, yielding bridged bicyclic compounds 85 and 87, respectively. Remarkably, the IEDDA cycloaddition of 3-carbomethoxy-2-pyrone 71a resulted in endo-specific compounds 85 (Scheme 19). This discovery contrasts sharply with 5-carbomethoxy-2-pyrone 12a, which typically produced a mixture of endo and exo isomers (Scheme 20). Furthermore, heating the resulting bridged bicyclic compounds 85 in toluene at 110 °C led to the formation of oxygenated cyclohexadienes 86 through CO<sub>2</sub> extrusion [29,30].



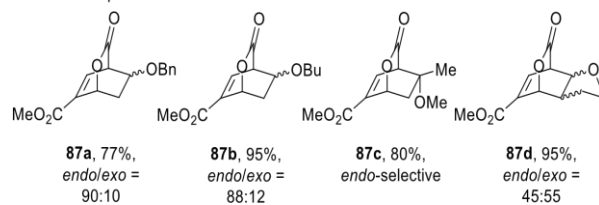
Substrate scope:



**Scheme 19. Thermal IEDDA Cycloaddition Of 3-Carbomethoxy-2-Pyrone with Vinyl Ethers**



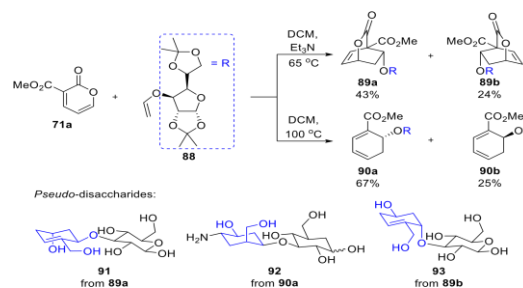
Substrate scope:



**Scheme 20. Thermal IEDDA Cycloaddition of 5-Carbomethoxy-2-Pyrone with Vinyl Ethers**

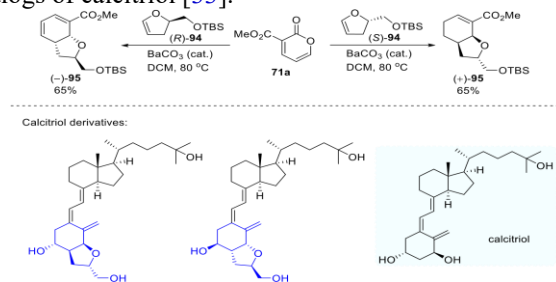
Oligosaccharides play numerous roles in vivo, including cell recognition and binding, and they have significant applications in clinical medicine. While various synthetic methods have been established for producing oligosaccharides, most involve late-stage coupling between pseudo-sugars and "true" sugars. To explore new strategies for synthesizing such pseudo-disaccharides, Afarinkia and colleagues examined the use of IEDDA cycloaddition of 3-carbomethoxy-2-pyrone to create pseudo-sugars. As illustrated in Scheme 21, vinylated sugar 88 acted as an electron-rich dienophile, participating in the thermal IEDDA cycloaddition with 3-carbomethoxy-2-pyrone 71a. By adjusting the reaction temperature, the IEDDA cycloaddition yielded bridged lactones 89 and cyclohexadienes 90. For instance, when the reaction was conducted at 65 °C in the presence of Et<sub>3</sub>N, bridged lactones 89a and 89b were obtained as diastereomers with isolated yields of 43% and 24%, respectively. In contrast, heating the mixture of 71a and 88 at 100 °C produced cyclohexadienes 90a and 90b with isolated yields of 67% and 25%, respectively. Ultimately, pseudo-disaccharides 91–93 were synthesized through further manipulation of these cycloadducts [31,32].





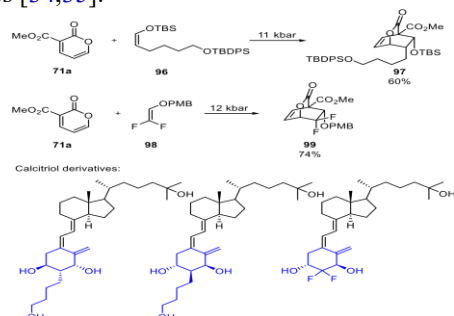
**Scheme 21. Thermal IEDDA Cycloaddition of 3-Carbomethoxy-2-Pyrone with Vinylated Sugar**

Calcitriol (1 $\alpha$ ,25-dihydroxyvitamin D3) is the active form of vitamin D used in clinical treatments to regulate calcium and phosphorus balance. To investigate the structure–activity relationship of calcitriol derivatives, researchers aimed to make minimal modifications to the cyclohexanol ring of calcitriol via an IEDDA cycloaddition of 3-carbomethoxy-2-pyrone with 1,2-disubstituted alkenes. In 2009, it was reported that 3-carbomethoxy-2-pyrone 71a underwent a diastereoselective IEDDA cycloaddition with enantioenriched 2,3-dihydrofurans (R)-94 and (S)-94 as dienophiles, resulting in cyclohexadienes (–)-95 and (+)-95 after CO<sub>2</sub> extrusion (Scheme 22). These cyclohexadienes were further converted into two tetrahydrofuran-fused analogs of calcitriol [33].



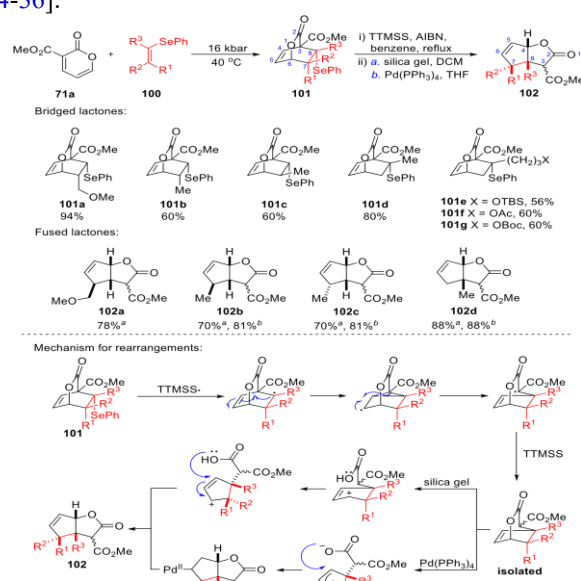
**Scheme 22. Thermal IEDDA Cycloaddition of 3-Carbomethoxy-2-Pyrone with Enantioenriched 2,3-Dihydrofurans.**

Posner and colleagues reported an intriguing example of the IEDDA cycloaddition of 2-pyrone involving an unconventional concerted mechanism under high pressure. As depicted in Scheme 23, 3-carbomethoxy-2-pyrone 71a underwent a high-pressure-promoted IEDDA cycloaddition with vinyl ethers 96 and 98, yielding racemic lactones endo-97 and endo-99 as the major products. The stereospecific formation of cis-97 indicated that the reaction occurred in a concerted manner rather than via the typical stepwise mechanism. Subsequent manipulation of these bridged bicyclic lactones led to the synthesis of various calcitriol derivatives [34,35].



**Scheme 23. High Pressure-Promoted IEDDA Cycloaddition Of 3-Carbomethoxy-2-Pyrone with Vinyl Ethers**

Vinylselenides, due to their similarities to oxygen, were also employed in reactions with 3-carbomethoxy-2-pyrone. This transformation was initially achieved through a high-pressure-promoted IEDDA cycloaddition of 3-carbomethoxy-2-pyrone 71a with various vinylselenides 100, resulting in bridged lactones 101 with complete regio- and endo-selectivity. Remarkably, the reaction exhibited diastereospecificity; for example, (Z)-vinylselenide 100b yielded cis-substituted bridged lactone 101b, whereas (E)-vinylselenide 100c produced trans-substituted bridged bicyclic lactone 101c. This behavior is consistent with the concerted mechanism typically observed in high-pressure-promoted IEDDA cycloadditions. The resulting bridged lactones 101 could be readily converted into the corresponding bicyclic fused lactones 102 via a two-step sequence involving radical-mediated and acid-catalyzed (or palladium-catalyzed) skeletal rearrangements (Scheme 24) [34–36].

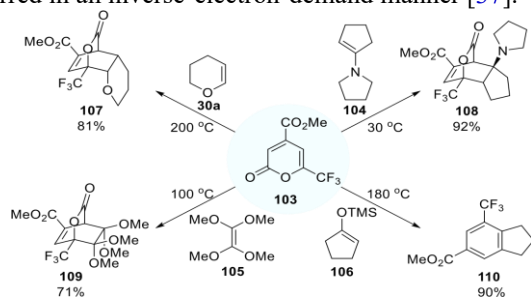


**Scheme 24. High Pressure-Promoted IEDDA Cycloaddition Of 3-Carbomethoxy-2-Pyrone with Vinylselenides.**

#### IEDDA Cycloaddition of 4-Carbonyl-2-Pyrone

As mentioned earlier, the challenge associated with the IEDDA cycloaddition of 2-pyrones containing an electron-withdrawing group at the C4 or C6 position stems from the relative instability of their reaction intermediates due to resonance stabilization. Furthermore, the limited availability of methods to prepare 4-carbonyl-substituted and 6-carbonyl-substituted 2-pyrones has hindered their use as electrophilic dienes in IEDDA cycloadditions. In 1985, an efficient synthesis method for 4-carbomethoxy-2-pyrone 103, featuring a trifluoromethyl group at the C6 position, was reported. This novel 2-pyrone 103 could serve as an electrophilic diene in thermal IEDDA cycloadditions with various alkenes, including 3,4-dihydro-2H-pyran 30a, N-pyrrolidino-1-cyclopentene 104, tetramethoxyethylene 105, and 1-trimethylsilyloxy-1-cyclopentene 106, predominantly yielding bridged lactones without CO<sub>2</sub> extrusion (Scheme 25).

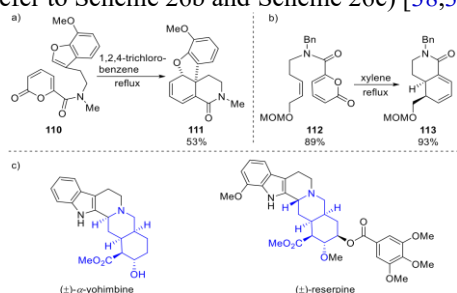
Importantly, electron-deficient dienophiles such as tetracyanoethylene and maleic anhydride did not react with 2-pyrone 103, indicating that this thermal [4+2] cycloaddition occurred in an inverse-electron-demand manner [37].



**Scheme 25. Thermal Cycloaddition Of 4-Carbomethoxy-2-Pyrone with Various Alkenes**

### IEDDA Cycloaddition of 6-Carbonyl-2-Pyrones

6-Substituted 2-pyrones often exhibit reduced reactivity towards nucleophilic attacks at the C6 position due to electronic effects and steric hindrance from the substituent at C6. However, this limitation can be overcome through the intramolecular cycloaddition of 2-pyrones containing a pendant alkene. Ciganek initially reported this reaction in 1981, demonstrating a thermal IEDDA cycloaddition of 2-pyrone-6-carboxamide 110 with a pendant benzofuran, leading to the formation of tetracyclic compound 111, as illustrated in Scheme 26a. Subsequently, Martin and colleagues employed a similar approach to synthesize the indole alkaloids (±)-yohimbine and (±)-reserpine, enabling the construction of a functionalized hydroisoquinoline subunit (refer to Scheme 26b and Scheme 26c) [38,39].

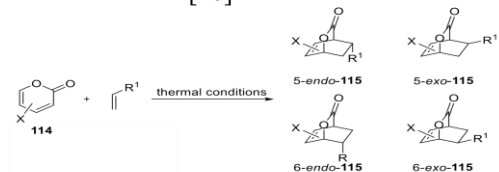


**Scheme 26. Thermal IEDDA Cycloaddition of 6-Carbonyl-2-Pyrones**

### IEDDA Cycloaddition of Bromo-Substituted 2-Pyrones

In 2005, the effects of halogen substituents (Cl, Br, I) at various positions on 2-pyrone were systematically studied. As depicted in Scheme 27, the cycloaddition of 2-pyrone with a bromine atom at the C3, C4, or C5 positions was carried out with different dienophiles under thermal conditions, resulting in multiple bridged bicyclic lactones. Interestingly, both 3-bromo-2-pyrone 114a and 5-bromo-2-pyrone 114b, synthesized easily through bromination of 5,6-dihydro-2H-pyran-2-one followed by oxidation, exhibited ambiphilic behavior. They could participate in IEDDA cycloaddition with electron-rich dienophiles and NEDDA cycloaddition with electron-poor dienophiles. In contrast, 4-bromo-2-pyrone 114c predominantly underwent NEDDA cycloaddition with electron-poor dienophiles. Additionally, the cycloaddition reactions involving 3-bromo-2-pyrone or 5-bromo-2-pyrone typically showed good regio- and stereoselectivity, favoring the formation of 5-endo cycloadducts. In comparison, reactions with 4-bromo-2-

pyrone exhibited good stereoselectivity but lacked regioselectivity, producing 5-endo and 6-endo cycloadducts in nearly equal amounts. Similar trends were observed with chloro- and iodo-substituted 2-pyrones. The regio- and stereoselectivity of these reactions were further elucidated using DFT calculations [40].



Dienophiles				
Dienes				
	80% <sup>a</sup> 75/0/25/0 <sup>b</sup>	78% <sup>a</sup> 65/14/11/10 <sup>b</sup>	18% <sup>a</sup> 100/0 <sup>c</sup>	65% <sup>a</sup> 68/32/0/0 <sup>b</sup>
	94% <sup>a</sup> 65/15/20/0 <sup>b</sup>	96% <sup>a</sup> 40/42/11/7 <sup>b</sup>	43% <sup>a</sup> 80/20 <sup>c</sup>	81% <sup>a</sup> 72/28/0/0 <sup>b</sup>
	78% <sup>a</sup> 43/7/45/5 <sup>b</sup>	75% <sup>a</sup> 39/5/35/21 <sup>b</sup>	7% <sup>a</sup> 100/0 <sup>c</sup>	-

<sup>a</sup>Yield. <sup>b</sup>Ratio of isolated cycloadducts 5-endo/5-exo/6-endo/6-exo. <sup>c</sup>Ratio of mixed cycloadducts endo/exo.

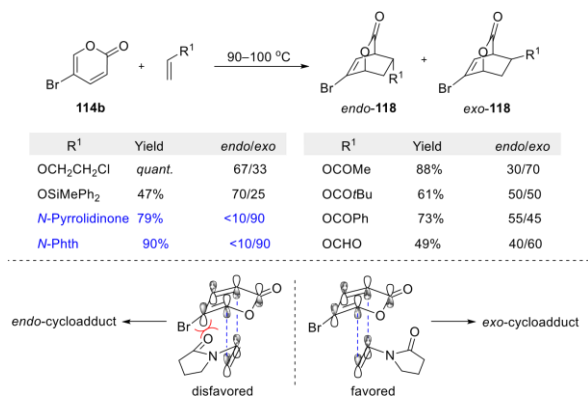
**Scheme 27. Thermal Cycloaddition of Bromo-Substituted 2-Pyrones with Various Alkenes**

While the type of halogen atom does not significantly influence the efficiency and selectivity of these reactions, bromo-substituted 2-pyrones have been more extensively researched than their chloro- and iodo-substituted counterparts in recent decades. This trend can be attributed to two main factors. Firstly, bromo-substituted 2-pyrones are generally easier to synthesize compared to chloro- and iodo-substituted variants. Secondly, the potential for late-stage reductive debromination of the resulting cycloadducts enables bromo-substituted 2-pyrones to function as synthetic equivalents of 2-pyrone, a capability demonstrated in various alkaloid total syntheses. The introduction of a bromine atom also enhances the reactivity of 2-pyrones. Typically, the reactivity order of bromo-substituted 2-pyrones is as follows: 3,5-dibromo-2-pyrone > 5-bromo-2-pyrone > 3-bromo-2-pyrone, which will be explored in subsequent sections [41].

### IEDDA Cycloaddition of 5-Bromo-2-Pyrones

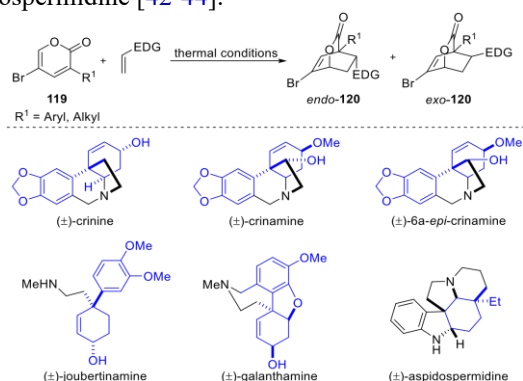
Initial studies focused on the efficiency and stereoselectivity of dienophiles in the thermal IEDDA cycloaddition involving 5-bromo-2-pyrone. As depicted in Scheme 28, altering the substituents on the dienophiles resulted in varying degrees of stereoselectivity, predominantly yielding either endo or exo cycloadducts. For example, vinyl ethers acted as nucleophilic dienophiles in reactions with 5-bromo-2-pyrone, primarily producing kinetically favored endo cycloadducts. Although exo cycloadducts are thermodynamically favored, their formation was hindered at higher temperatures due to additional CO<sub>2</sub> extrusion. In contrast, the cycloaddition of 5-bromo-2-pyrone with sterically hindered N-vinylpyrrolidinone or N-vinylphthalimide exhibited a strong preference for exo-selectivity, as steric factors impeded secondary orbital interactions [42].





**Scheme 28. Thermal IEDDA Cycloaddition of 5-Bromo-2-Pyrone with Electron-Rich Alkenes**

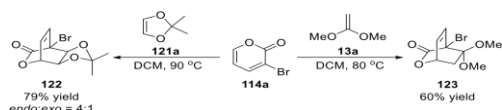
A similar reaction was developed using 5-bromo-2-pyrones with a substituent at the C3 position as the electrophilic diene (refer to Scheme 29). Subsequently, the synthetic utility of this approach was demonstrated through the total synthesis of several compounds, including (±)-joubertinamine, (±)-crinine, (±)-crinamine, (±)-6a-epi-crinamine, (±)-narwedine, (±)-lycoraminone, (±)-galanthamine, and (±)-aspidospermidine [42-44].



**Scheme 29. Thermal IEDDA Cycloaddition of 5-Bromo-2-Pyrone with Enol Ethers**

### IEDDA Cycloaddition of 3-Bromo-2-Pyrones

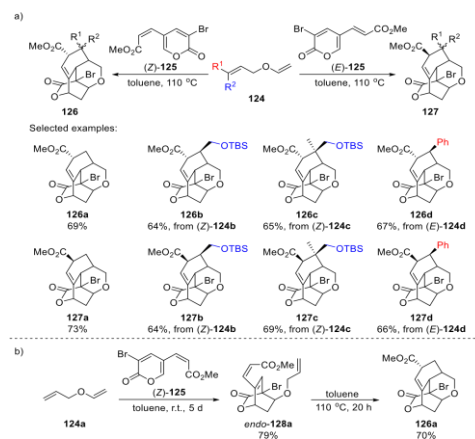
The first thermal IEDDA cycloaddition of 3-bromo-2-pyrone with electron-rich dienophiles occurred in 1991. This reaction involved 3-bromo-2-pyrone 114a reacting with 2,2-dimethyl-1,3-dioxole 121a and 1,1-dimethoxyethylene 13a under thermal conditions, leading to the formation of lactones 122-123 with high regioselectivity, as depicted in Scheme 30 [44].



**Scheme 30. Thermal IEDDA Cycloaddition of 3-Bromo-2-Pyrone with Electron-Rich Dienophiles**

Tandem DA cycloadditions have garnered significant synthetic interest over the past few decades due to their ability to increase molecular complexity in a single step rapidly. In 2006, it was reported that 3-bromo-5-vinyl-2-pyrones undergo tandem DA cycloaddition with allyl vinyl ethers 124 to produce various tetracyclic lactones. Significantly, the stereochemistry of the ester group in the final products was determined solely by the configuration of the acrylate fragment at the C5 position of the 3-bromo-2-pyrones. For example, the tandem DA cycloaddition of (Z)-125 with vinyl ethers 124 yielded tetracyclic lactones 126, whereas the

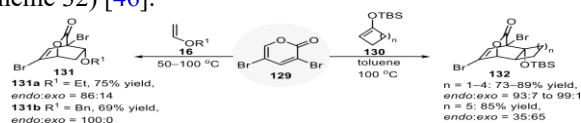
reaction of (E)-125 with the same vinyl ethers produced tetracyclic lactones 127. Additionally, the configuration of the allyl group in the dienophiles did not influence the orientation of substituents R1 and R2 in the resulting lactones (refer to Scheme 31a). By conducting the reaction at room temperature, lactone endo-128a was isolated, indicating that the first step involves an IEDDA cycloaddition. Heating lactone endo-128a in toluene at 110 °C resulted in the formation of tetracyclic lactone 126a (refer to Scheme 31b) [45].



**Scheme 31. Thermal Tandem DA Cycloaddition of 3-Bromo-5-Vinyl-2-Pyrones with Allyl Vinyl Ethers**

### IEDDA Cycloaddition of 3,5-Dibromo-2-Pyrone

Compared to monobromo-substituted 2-pyrone, 3,5-dibromo-2-pyrone exhibits higher reactivity and enhanced stereoselectivity in cycloadditions with both electron-rich and electron-poor dienophiles. Research on the synthesis and transformation of this synthon has been a focus for over a decade. In 2001, an efficient method was developed for synthesizing 3,5-dibromo-2-pyrone 129 through the bromo-decarboxylation of the corresponding carboxylic acid using NBS in a single step. Subsequently, the thermal IEDDA cycloaddition of 3,5-dibromo-2-pyrone 129 with vinyl ethers 16 and cycloalkenyl silyl ethers 130 was conducted, resulting in bridged bicyclic lactones 131-132 in good yields (refer to Scheme 32) [46].



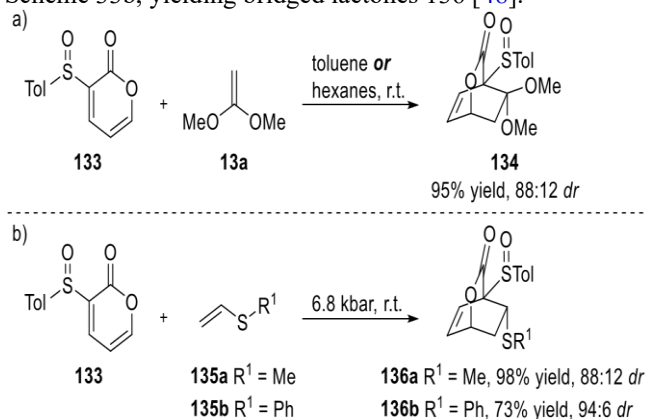
**Scheme 32. Thermal IEDDA Cycloaddition of 3,5-Dibromo-2-Pyrone with Electron-Rich Dienophiles**

### IEDDA Cycloaddition of Sulfur-Substituted 2-Pyrones

Sulfur-substituted 2-pyrones, such as 3-sulfinyl-2-pyrone and 3-sulfonyl-2-pyrone, serve as effective partners in IEDDA cycloadditions with electron-rich dienophiles. Due to their greater electronic deficiency compared to the corresponding 3-carbonyl-2-pyrone, 3-sulfinyl-2-pyrone and particularly 3-sulfonyl-2-pyrone can undergo cycloaddition with vinyl ethers and vinyl thioethers under milder conditions. This allows for the isolation of the resulting bridged bicyclic lactones without issues related to CO<sub>2</sub> extrusion or aromatization [47].

### IEDDA Cycloaddition of 3-Sulfinyl-2-Pyrone

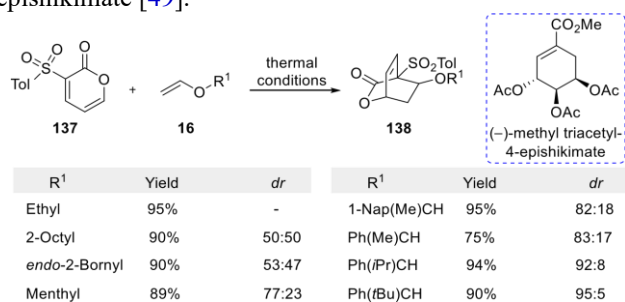
The first instance of the IEDDA cycloaddition involving 3-sulfinyl-2-pyrone **133** and 1,1-dimethoxyethylene **13a** occurred in 1985, resulting in the formation of bridged bicyclic lactone **134** in good yield (refer to Scheme 33a). Notably, the stereogenic sulfinyl group imparts a degree of diastereoselectivity, as the cycloadduct **134** was obtained as a mixture of two diastereomers (88:12 dr). Subsequently, the same research group broadened the substrate scope by employing vinyl thioethers **135** as electron-rich dienophiles under high pressure at room temperature, as illustrated in Scheme 33b, yielding bridged lactones **136** [48].



**Scheme 33. IEDDA Cycloadditions of 3-Sulfinyl-2-Pyrone with Electron-Rich Dienophiles**

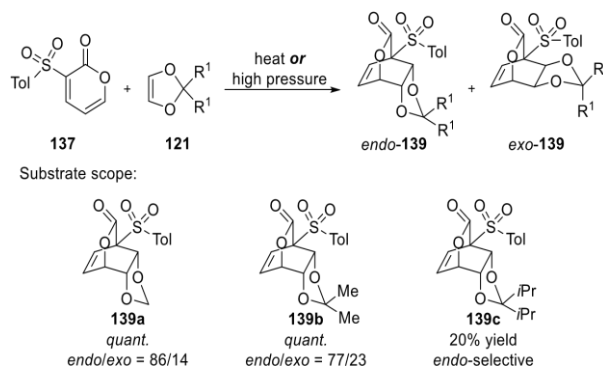
### IEDDA Cycloaddition of 3-Sulfonyl-2-Pyrone

In 1986, several optically active bridged bicyclic lactones **138** were synthesized using substrate-based asymmetric induction, where 3-sulfonyl-2-pyrone **137** underwent a highly diastereoselective IEDDA cycloaddition with vinyl ethers **16** (refer to Scheme 34). The resulting bridged bicyclic lactones served as precursors for the efficient preparation of enantioenriched polyfunctionalized cyclohexenes. The synthetic utility of this cycloaddition was demonstrated through the total synthesis of (–)-methyl triacetyl-4-epishikimate [49].



**Scheme 34. Thermal IEDDA Cycloaddition of 3-Sulfonyl-2-Pyrone with Enantioenriched Vinyl Ethers**

In 1990, an IEDDA cycloaddition involving 3-sulfonyl-2-pyrone **137** and electron-rich 1,3-dioxoles **121** was reported, resulting in the formation of bridged bicyclic lactones **139** (refer to Scheme 35). This cycloaddition could be initiated by either heating or applying high pressure. The reaction outcomes were significantly influenced by the steric hindrance of the dienophiles, with more sterically hindered 1,3-dioxoles, such as 2,2-diisopropyldioxole, exhibiting lower reactivity compared to unsubstituted 1,3-dioxole [49].

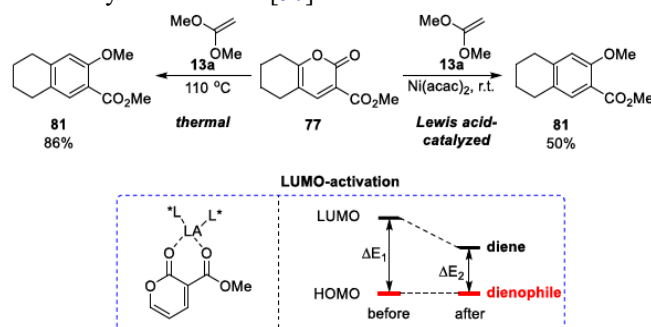


**Scheme 35. IEDDA Cycloaddition of 3-Sulfonyl-2-Pyrone with 1,3-Dioxoles**

### Catalytic IEDDA Cycloaddition

#### Lewis Acid-Catalyzed IEDDA Cycloaddition of 2-Pyrones

As previously noted, the [2.2.2]-bicyclic lactones formed from the IEDDA cycloaddition of 2-pyrones with dienophiles are often quite unstable under thermal conditions, leading to issues with CO<sub>2</sub> extrusion and subsequent aromatization. To prevent CO<sub>2</sub> loss from the initially formed cycloadducts, milder reaction conditions are necessary to replace the harsher conditions previously used. Since the first instance of a Lewis acid-catalyzed IEDDA cycloaddition of 2-pyrone was reported in 1984, chemists have recognized that Lewis acids can facilitate this reaction under gentler conditions. In that initial report, only the aromatic cycloadduct **81** was isolated when 5,6-disubstituted 3-carbomethoxy-2-pyrone **77** was reacted with 1,1-dimethoxyethylene **13a** in the presence of catalytic Ni(acac)<sub>2</sub> at room temperature. However, the yield was lower compared to the thermal IEDDA reaction (refer to Scheme 36). Generally, the role of the Lewis acid in the mild catalytic IEDDA cycloaddition is to lower the LUMO level of the 2-pyrone. Additionally, combining a Lewis acid with chiral ligands enables the asymmetric variant of the IEDDA cycloaddition, which cannot be achieved under non-catalytic conditions [50].

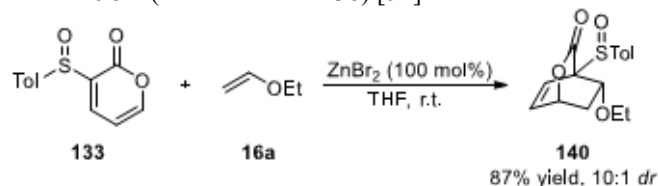


**Scheme 36. Comparable Results Between Thermal and Lewis Acid-Catalyzed IEDDA Cycloadditions**

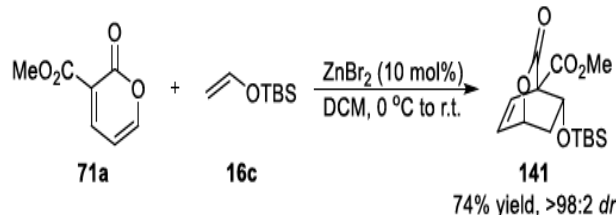
### Racemic IEDDA Cycloaddition of 2-Pyrones

In 1987, it was reported that the IEDDA cycloaddition of 3-sulfonyl-2-pyrone **133** with ethyl vinyl ether **16a** could be facilitated by zinc bromide at room temperature, resulting in bridged bicyclic lactone **140** in good yield (refer to Scheme 37). However, this reaction required a stoichiometric amount of zinc bromide.

In 2013, the same research group revealed that the IEDDA cycloaddition of 3-carbomethoxy-2-pyrone 71a with the more electron-rich silyl enol ether 16c could occur efficiently in the presence of a catalytic zinc salt, yielding bridged bicyclic lactone 141 in a 74% yield with a diastereomeric ratio of 98:2 (refer to Scheme 38) [51].

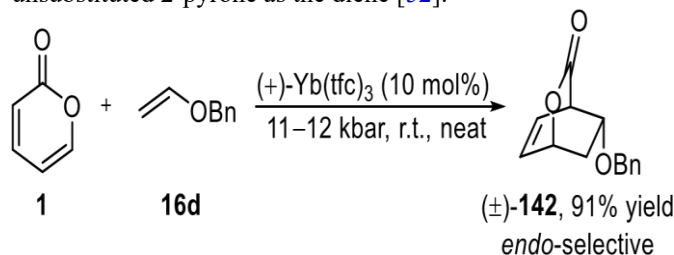


**Scheme 37. ZnBr<sub>2</sub>-Promoted IEDDA Cycloaddition of 3-Sulfinyl-2-Pyrone with Ethyl Vinyl Ether**



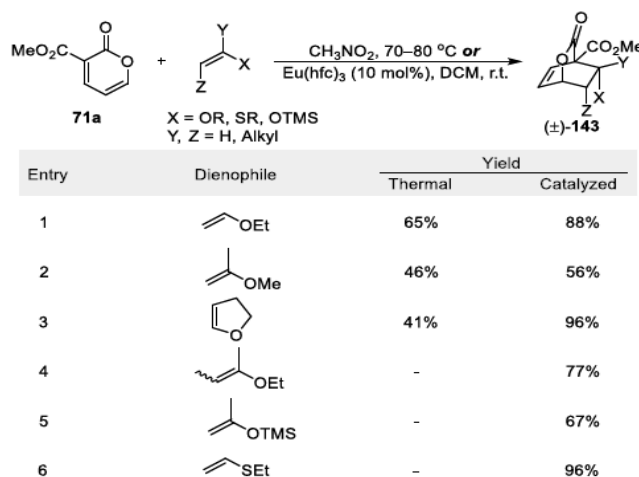
**Scheme 38. ZnBr<sub>2</sub>-Catalyzed IEDDA Cycloaddition of 3-Carbomethoxy-2-Pyrone with Silyl Enol Ether**

Lanthanides act as effective catalysts for the IEDDA cycloaddition of 3-carbomethoxy-2-pyrone with various electron-rich dienophiles. In 1994, it was reported that unsubstituted 2-pyrone 1 could undergo efficient IEDDA cycloaddition with electron-rich benzyl vinyl ether 16d using a combination of high pressure (11–12 kbar) and a catalytic amount of (+)-Yb(tfc)<sub>3</sub>. This resulted in the formation of racemic bridged bicyclic lactone 142 with complete regio- and diastereoselectivity (refer to Scheme 39). Control experiments underscored the importance of the reaction conditions, as undesired outcomes occurred at atmospheric pressure with a catalytic amount of (+)-Yb(tfc)<sub>3</sub> or under high pressure without the catalyst. Additionally, despite using chiral (+)-Yb(tfc)<sub>3</sub> as a catalyst, no asymmetric induction was observed. This finding is significant as it represents the first instance of a catalytic IEDDA cycloaddition employing unsubstituted 2-pyrone as the diene [52].



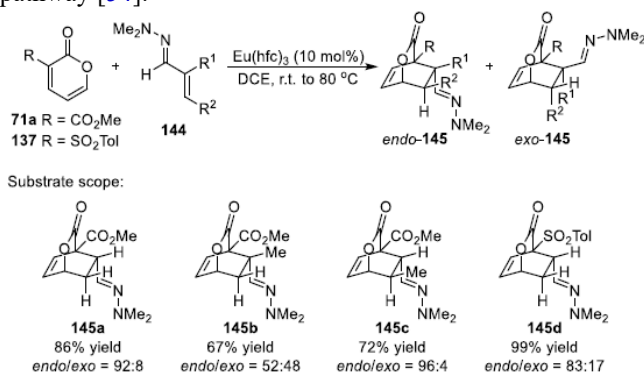
**Scheme 39. Yb(tfc)<sub>3</sub>-Catalyzed IEDDA Cycloaddition of 2-Pyrone with Benzyl Vinyl Ether**

In 1994, researchers investigated the Eu(hfc)<sub>3</sub>-catalyzed IEDDA cycloaddition of 3-carbomethoxy-2-pyrone 71a with electron-rich dienophiles, comparing it to the thermal IEDDA cycloaddition. As shown in Scheme 40, various dienophiles exhibited lower reactivities in the thermal IEDDA cycloaddition. However, with the addition of a catalytic amount of Eu(hfc)<sub>3</sub>, bridged bicyclic lactones 143 were obtained in good isolated yields using these dienophiles [53].



**Scheme 40. Comparable Results Between Thermal and Eu(hfc)<sub>3</sub>-Catalyzed IEDDA Cycloadditions of 3-Carbomethoxy-2-Pyrone**

In 2018, it was reported that an Eu(hfc)<sub>3</sub>-catalyzed IEDDA cycloaddition of 3-carbomethoxy-2-pyrone 71a or 3-sulfonyl-2-pyrone 137 with  $\alpha,\beta$ -unsaturated hydrazones 144 resulted in the formation of bridged bicyclic lactones 145 (see Scheme 41). The conversion of  $\alpha,\beta$ -unsaturated aldehydes to  $\alpha,\beta$ -unsaturated hydrazones facilitates umpolung, aligning the HOMO level of the resulting hydrazones with the LUMO level of electron-poor 2-pyrones. Conversely, when acrolein was directly used as the dienophile, no cycloaddition occurred, indicating an inverse-electron-demand reaction pathway [54].



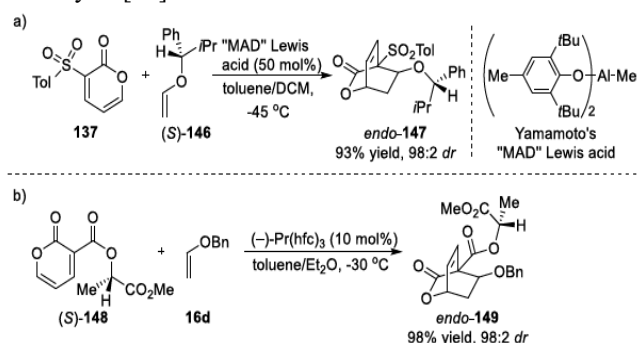
**Scheme 41. Eu(hfc)<sub>3</sub>-Catalyzed IEDDA Cycloaddition of 2-Pyrones with  $\alpha,\beta$ -Unsaturated Hydrazones**

### Diastereoselective IEDDA Cycloaddition of 2-Pyrones Using Chiral Auxiliaries

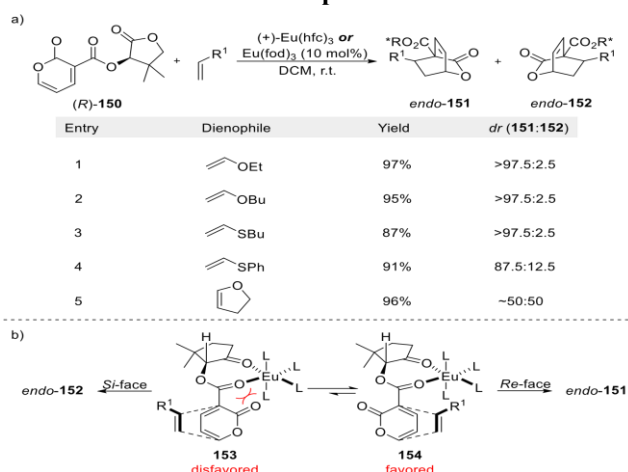
In 1990, enantioenriched vinyl ether (S)-146 was employed as the dienophile in an aluminum-catalyzed IEDDA cycloaddition with 3-sulfonyl-2-pyrone 137, yielding chiral bridged bicyclic lactone endo-147 as the major diastereomer. This reaction yielded a good result with excellent diastereoselectivity (see Scheme 42a). Subsequently, the same group developed an alternative method for synthesizing optically active bridged bicyclic lactones, using 2-pyrone 148 with a chiral side chain at the C3 position as the electrophilic diene in a catalytic IEDDA cycloaddition with benzyl vinyl ether 16d (see Scheme 42b) [54,55].



In 1994, the catalytic IEDDA cycloaddition of various chiral 3-carbonyl-2-pyrones was investigated, demonstrating that the (R)-pantolactone auxiliary produced excellent results in terms of both yield and diastereoselectivity. Mono-substituted dienophiles reacted with (R)-150 to yield bridged bicyclic lactones endo-151 as the predominant diastereomer, achieving good to excellent diastereoselectivities. Conversely, using dihydrofuran as the dienophile resulted in a nearly 1:1 mixture of diastereomers 151 and 152 (see Scheme 43a). Notably, the major diastereomer had the opposite absolute configuration compared to that reported by Posner et al. (endo-149, Scheme 43b), a phenomenon explained by the formation of chelated intermediates 153 and 154. Chelated intermediate 153 is less favored due to dipole-dipole repulsion between the two carbonyl groups on the same side. Moreover, the rigidity of the seven-membered ring in intermediates 153 and 154 prevents dienophiles from attacking the Si-face due to steric hindrance from the  $\alpha$ -methyl substituents. This chelated intermediate 154 also accounts for the similar levels of diastereoselectivity observed when using achiral  $\text{Eu}(\text{fod})_3$  and chiral (+)- $\text{Eu}(\text{hfc})_3$  as catalysts [56].



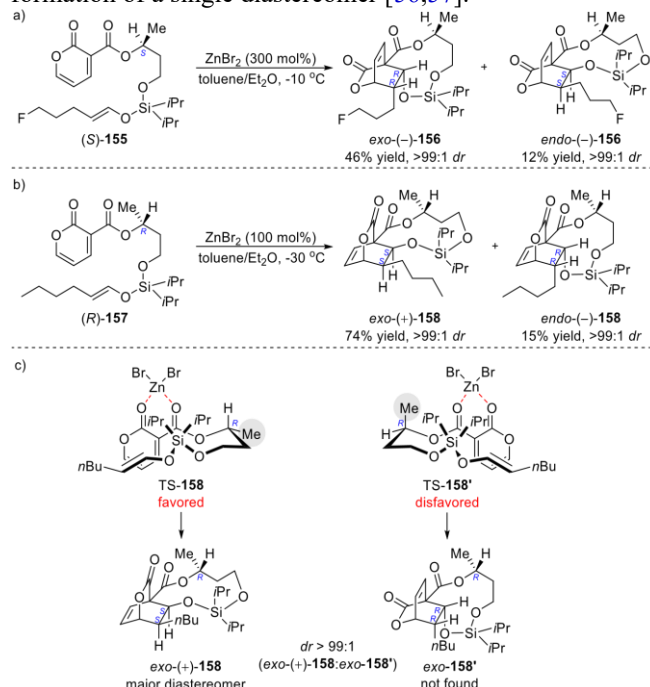
**Scheme 42. Diastereoselective IEDDA Cycloadditions by the Installation of a Chiral Auxiliary on 2-Pyrone or the Dienophile**



**Scheme 43. Diastereoselective IEDDA Cycloaddition of Chiral 3-Carbonyl-2-Pyrone with Various Dienophiles**

In 1995, Posner and colleagues investigated an intramolecular diastereoselective IEDDA cycloaddition of 2-pyrones, depicted in Scheme 44. The chiral 1,3-butanediol auxiliary acted as a linker between trans-silyl enol ethers and 2-pyrone-3-carboxylate. Zinc bromide facilitated the intramolecular IEDDA cycloaddition of the 2-pyrones (S)-155 and (R)-157 in a stepwise, asynchronous manner, exclusively yielding optically active cis-bridged lactones

with satisfactory exo/endo ratios. Notably, both exo and endo cycloadducts were diastereomerically pure (>99:1 dr), attributed to the orientation of the methyl group in the transition state. For instance, transition state TS-158, with the methyl group in a pseudo-equatorial position, exhibited greater stability compared to TS-158', where the methyl group was in a pseudo-axial position (see Scheme 44c). The energy disparity between these transition states favored the formation of a single diastereomer [56,57].

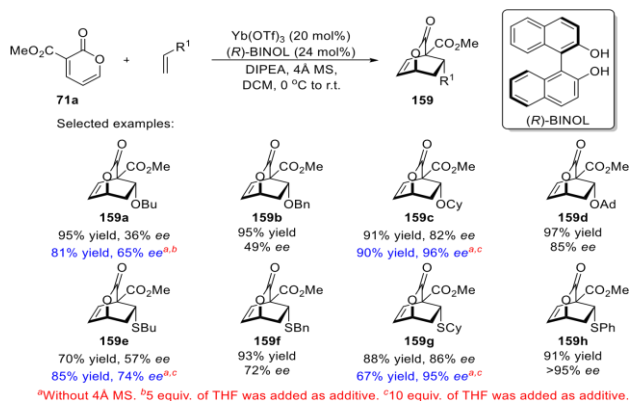


**Scheme 44. Intramolecular Diastereoselective IEDDA Cycloaddition of 2-Pyrones Bearing a Chiral Auxiliary**

### Enantioselective IEDDA Cycloaddition of 2-Pyrones

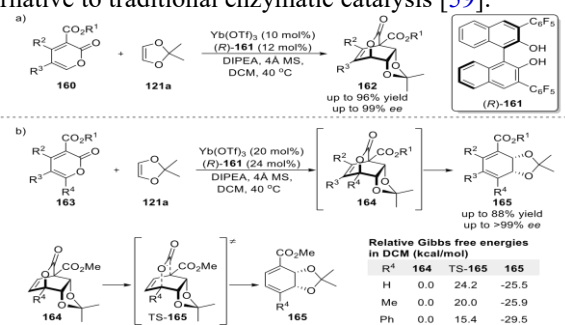
The highly diastereoselective catalytic IEDDA cycloaddition for synthesizing chiral bridged bicyclic lactones can be achieved using an auxiliary-based approach. However, this method is often burdened by the labor-intensive pre-installation and subsequent removal of the chiral auxiliary. Consequently, direct asymmetric induction through enantioselective catalysis has garnered significant research interest over the past few decades.

The first instance of a catalytic enantioselective IEDDA cycloaddition involving 3-carbomethoxy-2-pyrone with vinyl ethers and vinyl thioethers was accomplished by Markó and colleagues in 1994. Under the catalysis of  $\text{Yb}(\text{OTf})_3$  and (R)-BINOL, the reaction proceeded under mild conditions, yielding a variety of optically active bicyclic adducts 159 with varying enantioselectivities (see Scheme 45). Notably,  $\text{Yb}(\text{OTf})_3$  alone could not catalyze this cycloaddition effectively, indicating that a more efficient enantioselective catalyst was formed through the combination of  $\text{Yb}(\text{OTf})_3$  and (R)-BINOL. Later, the same group discovered that adding THF, without molecular sieves, significantly enhanced enantioselectivities in several cases, likely due to the formation of a new active ytterbium catalyst upon coordination with THF [57,58].



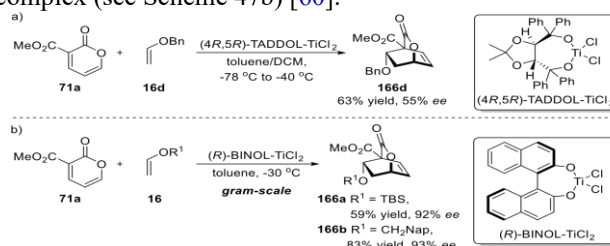
**Scheme 45. Enantioselective IEDDA Cycloaddition of 3-Carbomethoxy-2-Pyrone with Vinyl Ethers and Vinyl Thioethers**

More recently, Cai and colleagues developed an improved and efficient version of this reaction, yielding a series of bridged bicyclic lactones 162 and arene cis-dihydrodiols 165 in good yields with excellent enantioselectivities (see Scheme 46). After extensive screening of chiral ligands in conjunction with Yb(OTf)<sub>3</sub>, they discovered that introducing pentafluorophenyl groups at the 3,3'-positions of (R)-BINOL significantly increased both the yield and enantiomeric excess (ee) value. Notably, using a combination of Yb(OTf)<sub>3</sub> and chiral ligand (R)-161, the cycloaddition of 4,5-disubstituted-3-carboalkoxyl-2-pyrones 160 with 2,2-dimethyl-1,3-dioxole 121a proceeded effectively, producing bridged bicyclic lactones 162 with excellent enantioselectivities (see Scheme 46a). In contrast, the cycloaddition of the more sterically hindered 6-substituted-3-carboalkoxyl-2-pyrones 163 with 2,2-dimethyl-1,3-dioxole 121a did not yield bridged bicyclic lactones 164; instead, it generated arene cis-dihydrodiols 165 with excellent enantioselectivities (see Scheme 46b). The congested nature of the intermediates TS-165 and the stabilization of the C6-carbocation by substituents favored CO<sub>2</sub> extrusion under very mild conditions. DFT calculations indicated that increasing the size of R<sub>4</sub> lowered the energy barrier for CO<sub>2</sub> extrusion, aligning with experimental observations. The thermal CO<sub>2</sub> extrusion of bridged bicyclic lactones 162, derived from 4,5-disubstituted-3-carboalkoxyl-2-pyrones 160, needed to be performed in chlorobenzene at low concentrations to prevent dimerization of the resulting cyclohexadienes, allowing for the isolation of arene cis-dihydrodiols in good yields without loss of ee values. This method represents the first asymmetric chemical catalytic synthesis of arene cis-dihydrodiols and offers an efficient alternative to traditional enzymatic catalysis [59].



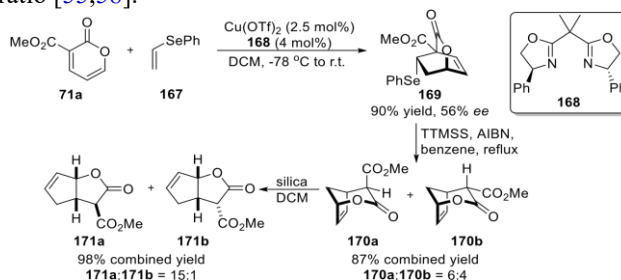
**Scheme 46. Enantioselective IEDDA Cycloaddition of 3-Carboalkoxyl-2-Pyrones with 2,2-Dimethyl-1,3-Dioxole**

In their study of enantioselective lanthanide catalysis, Posner and colleagues investigated the chiral titanium complex-promoted enantioselective IEDDA cycloaddition of 3-carbomethoxy-2-pyrone 71a with vinyl ethers 16. As illustrated in Scheme 47, the combination of Ti(OiPr)<sub>2</sub>Cl<sub>2</sub> and chiral diol ligands facilitated this cycloaddition in an enantioselective manner. For instance, using a stoichiometric (4R,5R)-TADDOL-TiCl<sub>2</sub> complex, the cycloaddition produced the optically active endo-adduct 166d, albeit with moderate yield and enantioselectivity (see Scheme 47a). Encouragingly, after extensive optimization of the reaction conditions, highly enantioenriched bridged bicyclic lactones 166a and 166b were successfully obtained on a gram scale using stoichiometric amounts of the chiral (R)-BINOL-TiCl<sub>2</sub> complex (see Scheme 47b) [60].



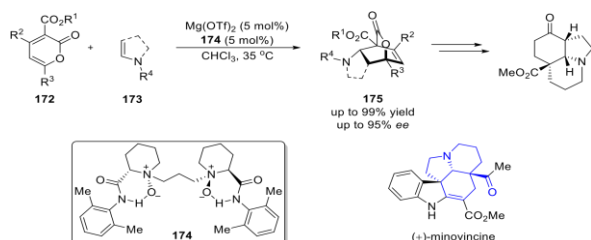
**Scheme 47. Enantioselective IEDDA Cycloaddition of 3-Carbomethoxy-2-Pyrone Promoted by Chiral Titanium Complex**

In 2000, it was reported that a combination of copper(II) triflate and chiral BOX ligand 168 was effective for the enantioselective catalytic IEDDA cycloaddition of 3-carbomethoxy-2-pyrone 71a with vinylselenide 167. This reaction yielded the corresponding bridged bicyclic lactone 169 in good isolated yield, albeit with moderate enantiomeric excess (ee) (see Scheme 48). The resulting bridged lactone 169 readily underwent a two-step sequence involving radical-mediated and acid-catalyzed skeletal rearrangements, producing bicyclic fused lactones 171a and 171b in a 15:1 ratio [55,58].



**Scheme 48. Enantioselective IEDDA Cycloaddition of 3-Carbomethoxy-2-Pyrone with Vinylselenide**

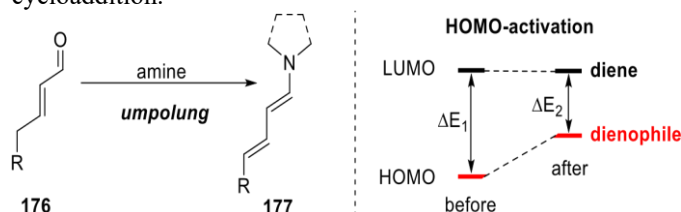
Recently, researchers developed a novel enantioselective catalytic system for the IEDDA cycloaddition of 2-pyrones 172 with achiral pyrroline derivatives 173, as depicted in Scheme 49. This reaction, catalyzed by a complex of Mg(OTf)<sub>2</sub> and chiral N,N'-dioxide ligand 174, yielded a variety of optically active bridged bicyclic adducts 175 with good to excellent enantioselectivities. Subsequent transformations of the resulting bridged lactones 175 enabled the formal synthesis of (+)-minovincine.



**Scheme 48. Enantioselective IEDDA Cycloaddition of 3-CARBOALKOXY-2-Pyrones with Pyrroline Derivatives**

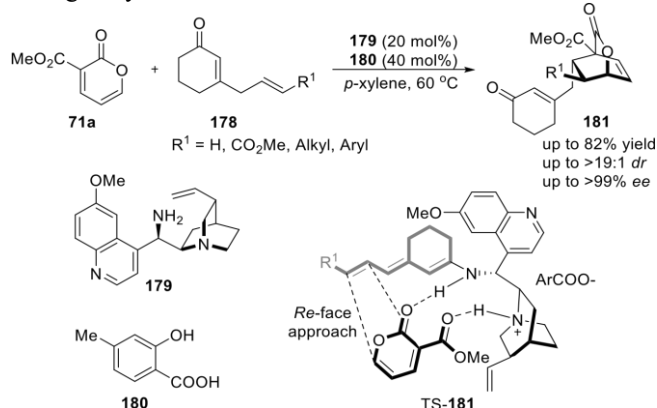
### Organocatalytic IEDDA Cycloaddition of 2-Pyrones

For decades, the catalytic IEDDA cycloaddition of 2-pyrones has primarily relied on a LUMO-activation strategy. Recently, however, significant interest has emerged in the chiral amine-catalyzed asymmetric IEDDA cycloaddition of  $\alpha,\beta$ -unsaturated carbonyl compounds, which operates on a HOMO-activation strategy. As depicted in Scheme 50, the condensation of  $\alpha,\beta$ -unsaturated carbonyl compounds 176 with chiral aminocatalysts generates dienamines 177, which serve as excellent intermediates for the IEDDA cycloaddition.



**Scheme 50. HOMO-Activation of  $\alpha,\beta$ -Unsaturated Carbonyl Compounds**

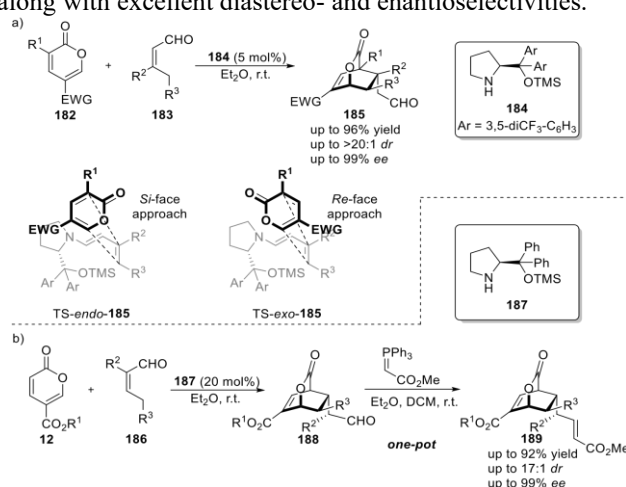
In 2018, the first example of organocatalytic asymmetric IEDDA cycloaddition involving 3-carbomethoxy-2-pyrone 71a was reported (see Scheme 51). Catalyzed by a primary amine 179 derived from cinchona alkaloid, trienamine intermediates were generated in situ from 2,5-dienones 178. The distal C–C double bond of these dienones underwent cycloaddition with 3-carbomethoxy-2-pyrone 71a from the Re-face, resulting in a series of bridged bicyclic lactones 181 with good yields and excellent diastereo- and enantiocontrol.



**Scheme 51. Organocatalytic Asymmetric IEDDA Cycloaddition of 3-Carbomethoxy-2-Pyrone with 2,5-Dienones**

Diarylprolinol silyl ethers have been extensively utilized as chiral organocatalysts for enantioselective transformations of aldehydes. Recently, Snyder and colleagues achieved a novel organocatalytic asymmetric IEDDA cycloaddition of electron-poor 2-pyrones 182 with 3,3-disubstituted  $\alpha,\beta$ -unsaturated aldehydes 183. As depicted in Scheme 52a, the reaction involved dienamine species generated in situ from

$\alpha,\beta$ -unsaturated aldehydes 183 through condensation with aminocatalyst 184, and electron-poor 2-pyrones 182. This yielded a variety of optically active bridged bicyclic lactones 185 in moderate to good yields (46–96%) and varying stereoselectivities (from 1.1:1 dr to >20:1 dr, 21% ee to 99% ee). Due to secondary orbital overlap between 2-pyrones and trienamines in transition state TS-endo-185, bridged bicyclic lactones endo-185 were obtained as the major diastereomer in all cases. The use of 3,3-disubstituted  $\alpha,\beta$ -unsaturated aldehydes was crucial for isolating the desired products. Subsequently, Albrecht and colleagues developed a similar reaction using 2,3-disubstituted  $\alpha,\beta$ -unsaturated aldehydes 186 as dienophiles (see Scheme 52b). However, the resulting bridged bicyclic lactones 188 were not stable enough for purification. Further transformation of cycloadducts 188 through a one-pot Wittig reaction enabled isolation of several corresponding  $\alpha,\beta$ -unsaturated esters 189 in good yields, along with excellent diastereo- and enantioselectivities.



**Scheme 52. Organocatalytic Asymmetric IEDDA Cycloadditions of 2-Pyrones with  $\alpha,\beta$ -Unsaturated Aldehydes**

### III. CONCLUSION

Advancements in the inverse-electron-demand Diels–Alder (IEDDA) cycloaddition of 2-pyrones mark a significant leap in synthetic organic chemistry. This review highlights the unique ambiphilic nature of 2-pyrones, which can react with both electron-rich and electron-poor dienophiles, thereby expanding the potential synthetic pathways. Our investigation into the underlying mechanisms reveals that the electronic properties of substituents have a critical influence on the reactivity and selectivity of these reactions. The evolution of methodologies—from non-catalytic to catalytic approaches, including microwave-assisted techniques and high-pressure conditions—has further bolstered the efficiency and versatility of IEDDA cycloadditions. The synthesis of chiral bridged bicyclic lactones using substituted 2-pyrones highlights the practical applications of these reactions in constructing complex molecular architectures. As the field progresses, insights gleaned from these studies are poised to inspire novel strategies for synthesizing valuable natural products and functional materials.



The significance of IEDDA cycloaddition in advancing organic synthesis cannot be overstated, as it lays the groundwork for innovative approaches in chemical research and applications.

### DECLARATION STATEMENT

I must verify the accuracy of the following information as the article's author.

- **Conflicts of Interest/Competing Interests:** Based on my understanding, this article has no conflicts of interest.
- **Funding Support:** This article has not been sponsored or funded by any organization or agency. The independence of this research is a crucial factor in affirming its impartiality, as it was conducted without any external influence.
- **Ethical Approval and Consent to Participate:** The data provided in this article is exempt from the requirement for ethical approval or participant consent.
- **Data Access Statement and Material Availability:** The adequate resources of this article are publicly accessible.
- **Author's Contributions:** The authorship of this article is contributed solely.

### REFERENCES

1. Machkour A, Thallaj NK, Benhamou L, Lachkar M, Mandon D. Chemistry. 2006 Aug 25;12(25):6660-8. P 6660-6661-6662-6663.
2. Thallaj, N., Machkour, A., Mandon, D., Welter, R., New. J. Chem., 2005, 29, 1555 – 1558.
3. Thallaj NK, Rotthaus O, Benhamou L, Humbert N, Elhabiri M, Lachkar M, Welter R, Albrecht-Gary AM, Mandon D. Chemistry. 2008;14(22):6742-53. P6745-6746-6747.
4. Wane A, Thallaj NK, Mandon D. Chemistry. 2009 Oct 12;15(40):10593-602. P10594-10595-10595.
5. Thallaj NK, Orain PY, Thibon A, Sandroni M, Welter R, Mandon D. Inorg Chem. 2014 Aug 4;53(15):7824-36. P7826-7827-7828.
6. N. K. Thallaj, J. Przybilla, R. Welter and D. Mandon, J. Am. Chem. Soc. 2008, 130, 2414-2415.
7. N. K. Thallaj, D. Mandon and K. A. White, Eur. J. of Inorg. Chem., 2007, 44–47.
8. Thallaj, N.; International journal of applied chemistry and biological sciences 2021, 2 (4), 65-77.
9. Thallaj, N.; Indian Journal of Advanced Chemistry (IJAC) 2021, 1 (2), .
10. Thallaj, N.; International Journal of Research Publication and Reviews (IJRPR) 2021, 2, 10, 951-959
11. L. Labban, N. Thallaj, Z. Malek; International Journal of Medical Studies, 2020, 5, No 12, 23-36.
12. L. Labban, M. Kudsi, Z. Malek, N. Thallaj; Advances in Medical, Dental and Health Sciences, 2020, 3, 3, 45-48.
13. L. Labban, N. Thallaj, M. Al Masri; Journal of Advanced Research in Food Science and Nutrition, 2020, 3, 1, 34-41.
14. L. labban; N. thallaj; A. labban; archives of medicine, 2020, 12, 2:8, 1-5.
15. L. labban; N. thallaj; international journal of herbal medicine, 2020, 8, 2, 33-37.
16. L. Labban, N. Thallaj, Z. Malek; Journal of Medical Research and Health Sciences, 2019, 2, 11, 784-787.
17. L. labban N. Thallaj; acta scientific nutritional health, 2019, 3, 10, 7-12.
18. Malek, Z.S.; Sage D.; Pevet, P.; Raison, S.; Endocrinology 2007, 148 (11), 5165-5173.
19. Malek, Z.S.; Dardente, H.; Pevet, P.; Raison, S.; European Journal of Neuroscience 2005, 22 (4), 895-901.
20. Malek, Z.S.; Pevet, P.; Raison, S.; Neuroscience 2004, 125 (3), 749-758.
21. Malek, Z.S.; Labban, L.; The International Journal of Neuroscience, 2020, 1-7.
22. Malek, Z.S.; Labban, L.; European Journal of Pharmaceutical and Medical Research 2019, 6 (11), 527-532.
23. Malek, Z.S.; Journal of AlBaath University 2018, 40 (4), 39-62.
24. Malek, Z.S.; Tishreen University Journal for Research and Scientific Studies, 2018, 40.
25. ZS Malek, LM Labban; International Journal of Neuroscience, 2021, 131 (12), 1155-1161.
26. ZS Malek, LM Labban; Journal of current research in physiology and pharmacology, 2020, 4, (1), 1-5.
27. L.M. Labban, M. M. Alshishkli, A. Alkhalaf, Z. Malek; J. Adv. Res. Dent. Oral Health, 2017, 2(3&4), 1-4.
28. L Labban, ZS Malek, Open Access Library Journal, 2018, 5 (07), 1-11.
29. L Labban, ZS Malek, Ann Food Nutr Res J, 2019, 1, 1.
30. Labban, L. and N. Thallaj, 2019. Acta Scient. Nutr. Health, 3: 7-12.
31. Y. alhomush, Z. malek, A. Abboud, N. Thallaj, Research Journal of Pharmacy and Technology, 2022, 15, 10.
32. Thallaj, Nasser. "تخليق مشتقات 1، 3، 4-أوكساديازول، ثيازوليدين بمساعدة المايكرويف." Tishreen University Journal-Medical Sciences Series 44.1 (2022): 59-77.
33. N. Thallaj, Tishreen university journal, 2022, 44, 2, 87-105.
34. N. Thallaj. Indian Journal of Advanced Chemistry, 1 (3), 2022. 10-14.
35. Thallaj, Nasser. "Characterization of charge heterogeneity of antibody-drug conjugate by anion-exchange chromatofocusing." Tishreen University Journal-Medical Sciences Series 44.6 (2022): 21-29.
36. A. Abboud, Z. Malek, N. Thallaj. 2022 15, 11, 4935-4939. Research Journal of Pharmacy and Technology.
37. L. Alallan, Z. malek, (2023). 45, (1) 73-81. Tishreen University Journal-Medical Sciences Series.
38. Thallaj, Nasser, and Mays Khazem. "Studying the efficacy of the plant extract of Tetracera scandens as an antidiabetic treatment." Tishreen University Journal-Medical Sciences Series 45.1 (2023): 33-44.
39. N. Thallaj. International Journal of Advanced Pharmaceutical Sciences and Research (IJAPSR) 2022. 2, 3, 1-28
40. N. Thallaj. International Journal of Advanced Pharmaceutical Sciences and Research (IJAPSR) 2022. 2, 4, 1-15.
41. N. Thallaj. International Journal of Advanced Pharmaceutical Sciences and Research (IJAPSR) 2022. 2, 6, 1-12.
42. Thallaj, Nasser. "Review of a Few Selected Examples of Intermolecular Dioxygenases Involving Molecular Oxygen and Non-Heme Iron Proteins." Int. J. Adv. Pharmacol. Sci. Res. (IJAPSR) 3 (2023): 1-18.
43. Thallaj, Nasser, and Ayat Abboud. "مقارنة بين مرتسمات الكروماتوغرافيا البؤرية لمغاريات الشحنة لأعداد وحيدة التسيلة عارية ومرتبطة مع دواء cIEF." Tishreen University Journal-Medical Sciences Series 45.2 (2023): 47-57.
44. Dayoub, Leen, Yanal Alkuddsi, and Nasser Thallaj. "Investigating the interaction between some of Bipolaris sorokiniana's toxins and the Gα Subunit of the Wheat G-Protein using bioinformatics tools." University of Thi-Qar journal of agricultural research 12.1 2023..
45. Thallaj, N; agha, M. I .H.; nattouf; A.H; katib, CH; karaali, A; Moustapha, A; Labban L; open access library journal, 2020, 7, 5, 1-21..
46. N. Thallaj. Indian Journal of Advanced Chemistry, 1 (3), 2022. 10-14.
47. N. Thallaj. Xi'an Shiyoudaxue Xuebao (Ziran Kexue Ban)/ Journal of Xi'an Shiyou University, Natural Sciences Edition. 2022. 65, 06. 289-301.
48. N. Thallaj. Xi'an Shiyoudaxue Xuebao (Ziran Kexue Ban)/ Journal of Xi'an Shiyou University, Natural Sciences Edition. 2022. 65, 06. 313-328.
49. Z. MALEK, A. ABBOOD, N. THALLAJ. Xi'an Shiyoudaxue Xuebao (Ziran Kexue Ban)/ Journal of Xi'an Shiyou University, Natural Sciences Edition. 2022. 65, 06. 302-312.
50. N. Thallaj. 2022. 65, 7, 169-184. Xi'an Shiyoudaxue Xuebao (Ziran Kexue Ban)/ Journal of Xi'an Shiyou University, Natural Sciences Edition.
51. N. Thallaj. 2022. 65, 7, 110-142. Xi'an Shiyoudaxue Xuebao (Ziran Kexue Ban)/ Journal of Xi'an Shiyou University, Natural Sciences Edition.
52. N Thallaj, (2023). 44, (6), 21-29. Tishreen University Journal-Medical Sciences Series.
53. N. Thallaj. International Journal of Advanced Pharmaceutical Sciences and Research (IJAPSR) 2022. 2, 6, 1-12.
54. N. Thallaj. International Journal of Advanced Pharmaceutical Sciences and Research (IJAPSR) 2023. 3, 3, 1-10.
55. N. Thallaj. International Journal of Advanced Pharmaceutical Sciences and Research (IJAPSR) 2024. 4, 1, 32-52.
56. N. Thallaj. International Journal of Advanced Pharmaceutical Sciences and Research (IJAPSR) 2024. 4, 3, 6-19.
57. N. Thallaj. International Journal of Advanced Pharmaceutical Sciences and Research (IJAPSR) 2024. 4, 4, 7-21.

58. Besherb S, Alallan L, Hassan Agha MA, Alshamas I, Thallaj N. Influence of soil salinity on the chemical composition of essential oil of *Rosmarinus Officinalis* in Syria, *Research J. Pharm. and Tech.* 2024; 17(4).
59. Isbera M, Abbood A, Ibrahim W. Weight and Content Uniformity of Warfarin Sodium Half Tablets. *Research J. Pharm. and Tech.* 2016; 9(3):215-218. doi: 10.5958/0974-360X.2016.00039.1
60. Abbood A, Layka R. Weight and content uniformity Study of captopril half-tablets. *Research J. Pharm. and Tech.* 2017;10(6):1621-1626. doi: 10.5958/0974-360X.2017.00285.2.

## AUTHOR PROFILE



**Prof. Dr. Nasser Thallaj, 2020-** present time: Professor in the biomedical Science program.

2020- Present time: *Assistant professor* position. Faculty of Pharmacy, Al-Rashed University, Damascus, Syria.

From 15 June 2019 – 31 July 2020: President of *AlJazeera University*, Damascus, Syria.

From April 1st, 2019 – 15 June: vice president for scientific affairs and Dean of the Faculty of pharmacy, Al Jazeera University, Damascus, Syria.

From October 1<sup>st</sup> 2018-15 march 2020: Dean of the Faculty of pharmacy, *Al Jazeera University*, Damascus, Syria.

2017-31 July2020: *Assistant professor* position. Faculty of Pharmacy, *Al Jazeera University*, Damascus, Syria

- 2015-2017: *Assistant professor* position. Faculty of Pharmacy, *Syrian Private University*, Damascus, Syria

- 2015- 2016: Consultant in Ugarit Education Group: foundation of *AlManara University*.

- 2014-2015: vice president for scientific affairs (in charge), *University of Kalamoon*, Dier Attieh, Syria.

- 2014-2015: In charge of higher education affairs, *University of Kalamoon*, Dier Attieh, Syria.

- 2012-2014: Dean of the Faculty of Applied Sciences, *University of Kalamoon*. Dier Attieh, Syria.

- 2010-2013: Head of the Department of Chemistry. Faculty of Applied Sciences, *University of Kalamoon*. Dier Attieh, Syria

-2008: *Assistant professor* position. Faculty of Applied Sciences, *University of Kalamoon*. Dier Attieh, Syria

2007-2008: Post-Doctoral position. *Laboratory of NanoOrganic Chemistry and Supramolecular Materials*, thesis title: *Drug Delivery System*, Department of Chemistry. *University Notre Dame de la Paix*. Namur, Belgium.

**Disclaimer/Publisher's Note:** The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of the Lattice Science Publication (LSP)/ journal and/ or the editor(s). The Lattice Science Publication (LSP)/ journal and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions, or products referred to in the content.