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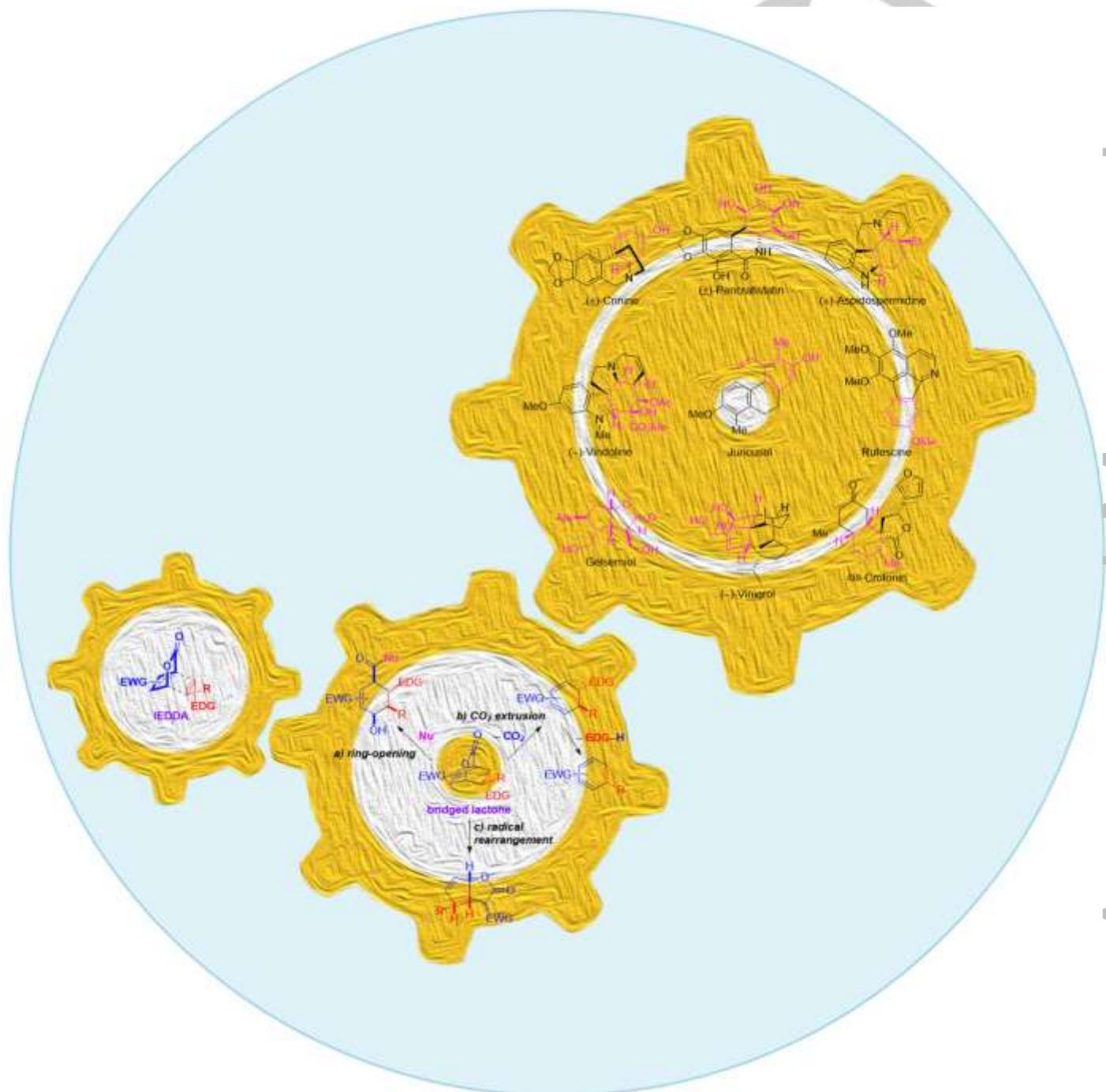
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Inverse-Electron-Demand Diels–Alder Reactions of 2-Pyrones: Bridged Lactones and Beyond

Guanghao Huang, Cyrille Kouklovsky, and Aurélien de la Torre*^[a]

Dedication ((optional))



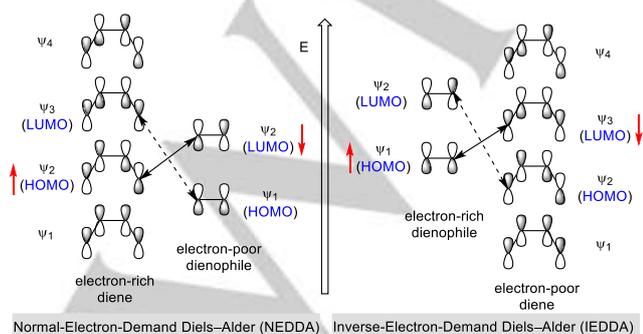
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Abstract: Inverse-electron-demand Diels–Alder (IEDDA) reactions of electron-poor 2-pyrones as electrophilic dienes have been extensively studied in the past fifty years. These reactions provide an efficient access to bridged bicyclic lactones and their derivatives, such as densely functionalized 1,3-cyclohexadienes after CO₂ extrusion and polysubstituted aromatic compounds through elimination. This reaction has been used for the synthesis of many biologically active natural products and drug candidates. In this review, the developments of these IEDDA reactions including non-catalytic, Lewis acid-catalyzed and organocatalytic IEDDA reactions, and their applications in total synthesis are discussed in detail.

1. Introduction

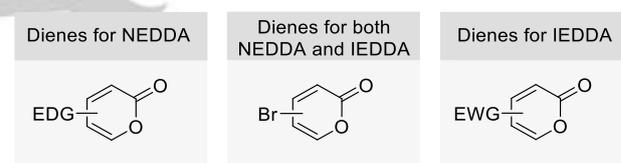
In the past nearly 100 years, the Diels–Alder (DA) reaction has proved its potential for the synthesis of natural products^[1] and multifunctional materials^[2] since the first case reported by Otto Diels and Kurt Alder in 1928.^[3] The great success of DA reaction is attributed to its high efficiency to construct a six-membered ring with four contiguous stereocenters in a single step, as well as its good regio- and stereoselectivity, which stimulated chemists to explore the internal molecular mechanism to understand how DA reaction proceeds and to further predict new reactions.

The Frontier Molecular Orbital (FMO) theory is a classical model describing HOMO/LUMO interactions, in which DA reactions can be classified into two types (Scheme 1).^[4] The first type is normal-electron-demand Diels–Alder (NEDDA) reactions involving [4+2] cycloadditions of electron-rich dienes and electron-poor dienophiles. The second type of [4+2] cycloadditions employing electron-poor dienes and electron-rich dienophiles is inverse-electron-demand Diels–Alder (IEDDA) reactions. Generally, electron-donating group can raise the HOMO level, and in contrast electron-withdrawing group can lower the LUMO level.



Scheme 1. Difference between NEDDA and IEDDA reactions in π molecular orbitals.

Despite its aromaticity, 2-pyrone can be treated as a 1,3-butadiene bearing an electron-withdrawing carboxyl group on one side and an electron-donating acyloxy group on the other side. Therefore, 2-pyrone can react with both electron-rich and electron-poor dienophiles, making them ambiphilic. However, the cycloaddition of unsubstituted 2-pyrone is usually plagued by self-polymerization under thermal conditions.^[5] Fortunately, substituted 2-pyrones are suitable for DA reactions, and the electronic property of the substituent on the pyrone ring decides which type of DA reaction happens. It has been recognized that electron-rich 2-pyrones are good dienes for NEDDA reactions. On the other hand, electron-poor 2-pyrones participate in IEDDA reactions as electrophilic dienes with higher reactivity because the electron-withdrawing group on the pyrone ring destroys the internal electron delocalization (less aromaticity) and lowers the LUMO level. It should be noted that bromo- and dibromo-substituted 2-pyrones can carry out both NEDDA reactions and IEDDA reactions flexibly (Scheme 2).^[6]



Scheme 2. Ambiphilic capacity of 2-pyrones.

In the past few decades, much effort has been focused on the development of methodologies for IEDDA reactions and their synthetic applications. Among those, 2-pyrone derivatives captured the attention of chemists, due to the synthetic attractiveness of the resulting bridged bicyclic lactones and their derivatives, such as densely functionalized 1,3-cyclohexadienes after CO₂ extrusion and polysubstituted aromatic compounds through the loss of a small molecule. Although there have been a number of excellent reviews on different classes of IEDDA reactions,^[7] there are only few reviews on IEDDA reactions of 2-pyrones.^[8] Since then, many advances were reported. In particular, catalytic IEDDA reactions by Lewis acids and organocatalysts allowing efficient preparation of various chiral bicyclic lactones not accessible by non-catalytic IEDDA reactions have attracted much attention in the past 30 years. Moreover, numerous synthetic applications for these IEDDA reactions have emerged in the last 20 years. Therefore, we will herein focus on IEDDA reactions of 2-pyrones as electrophilic dienes with alkenes, covering the literature up to August 2020. This review begins with a brief description about the mechanism of IEDDA reactions of electrophilic 2-pyrones (Section 2) and then individually discusses non-catalytic, Lewis acid-catalyzed and organocatalytic IEDDA reactions of electrophilic 2-pyrones (Sections 3 and 4). Finally, the application of these reported

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methodologies to the total synthesis of natural products and drug candidates will be reviewed in a last part (Section 5).

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Cyrille Kouklovsky was born in Paris, France. He completed his PhD at Université Paris-Sud in 1989 under the supervision of Prof. Y. Langlois before doing postdoctoral studies with Prof. Steven V. Ley at University of Cambridge. He is currently a full professor of organic chemistry at Université Paris-Saclay. His research interests include asymmetric dipolar cycloaddition reactions and their synthetic applications. He was the president of the Organic Chemistry Division of the French Chemical Society from 2015 to 2019.



Aurélien de la Torre studied chemistry in Montpellier and obtained his PhD in 2014 under the supervision of Dr. Jean-Marie Galano and Dr. Camille Oger. After two postdoctoral positions in the groups of Prof. Nuno Maulide (University of Vienna) and Prof. Ilan Marek (Technion – Israel Institute of Technology), he was appointed in 2018 as Chargé de Recherche CNRS. His research interests include total synthesis, cascade rearrangements and cycloaddition reactions.

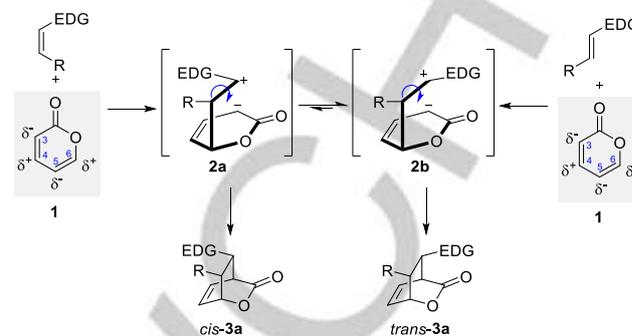


2. Mechanism

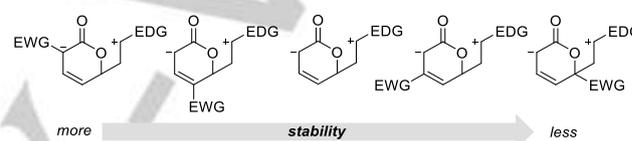
The electron density distribution of 2-pyrone and its derivatives is shown in Scheme 3, indicating that C-3 and C-5 positions have a large electron density but C-4 and C-6 positions have a deficiency of electron density. Therefore, 2-pyrone is electrophilic at C-6 position and nucleophilic at C-3 position, making it an excellent diene for IEDDA reactions.

It is widely recognized that DA reactions between highly polarized 2-pyrone derivatives and dienophiles proceed in a stepwise fashion instead of a conventional concerted fashion, as shown in Scheme 3.^[9] Indeed, the reaction of a *Z* or *E* dienophile with 2-pyrone **1** under thermal or catalytic conditions usually results in the formation of *trans*-**3a** as a major product. This can be explained by the formation of intermediate **2**, which in the case of a *Z* dienophile rotates from conformer **2a** to more stable conformer **2b**, ultimately affording product *trans*-**3a**. From the perspective of electron density, electron-withdrawing groups on the pyrone ring can accelerate IEDDA reactions. Meanwhile,

reaction intermediates from 3-substituted and 5-substituted 2-pyrones are more stable than those from 4-substituted and 6-substituted 2-pyrones in agreement with resonance stabilization (Scheme 4), which is consistent with the observed results of IEDDA reactions of substituted 2-pyrones.

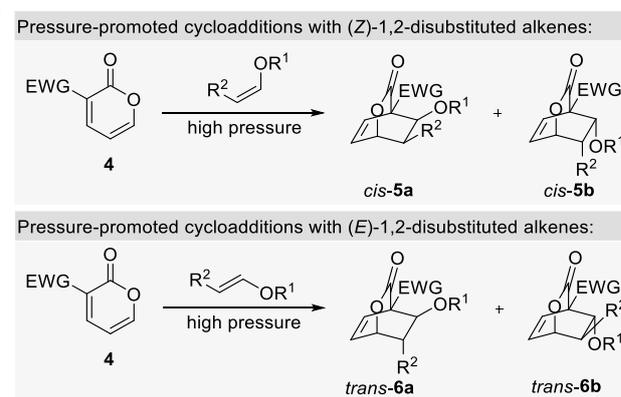


Scheme 3. Stepwise mechanism of IEDDA reactions of 2-pyrone.



Scheme 4. Comparison of stability between different reaction intermediates.

On the other hand, Posner and Cho pointed out that high pressure-promoted IEDDA reactions of 3-substituted 2-pyrones occurred in a concerted fashion. They observed that *cis* products **5** were obtained exclusively from cycloadditions of 3-substituted 2-pyrones **4** with (*Z*)-1,2-disubstituted alkenes and only *trans* products **6** were isolated from cycloadditions of 3-substituted 2-pyrones **4** with (*E*)-1,2-disubstituted alkenes under high pressure (Scheme 5).



Scheme 5. Stereospecificity of IEDDA reactions under high pressure.

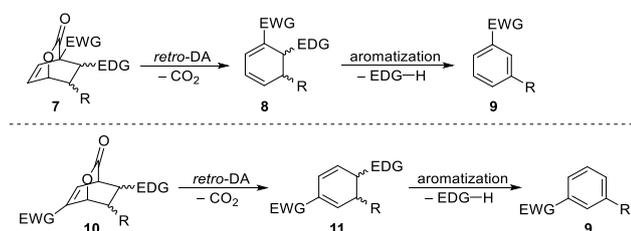
3. Non-catalytic IEDDA reactions

Non-catalytic IEDDA reactions of electrophilic 2-pyrones have been frequently investigated in the past 50 years, the dienes of which mainly include carbonyl-substituted 2-pyrones, bromo-substituted 2-pyrones and sulfur-substituted 2-pyrones. For

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dienophiles, ketene acetals, enamines, and vinyl ethers are commonly used for such IEDDA reactions. These protocols could be promoted by direct heating or by high pressure. It should be noted that initially formed bridged bicyclic products are unstable at high temperatures, and CO₂ extrusion occurs through *retro*-DA reactions to provide highly functionalized cyclohexadienes which can be further converted into a series of substituted arenes by loss of small molecules (Scheme 6).



Scheme 6. Conversion of bridged bicyclic products under thermal conditions.

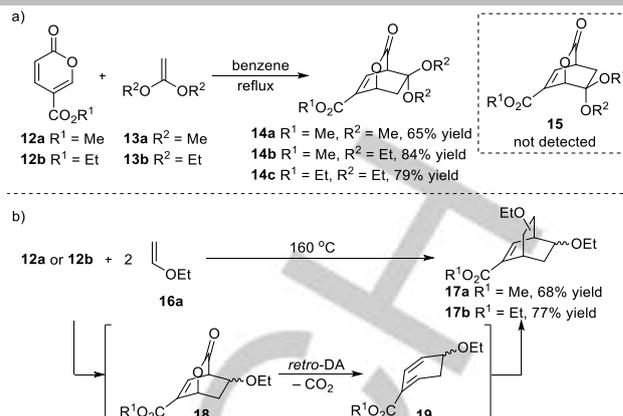
In recent years, the emergence of microwave technology as well as the use of new dienophiles lead to many advances, which will be reported in this section.

3.1. IEDDA reactions of carbonyl-substituted 2-pyrones

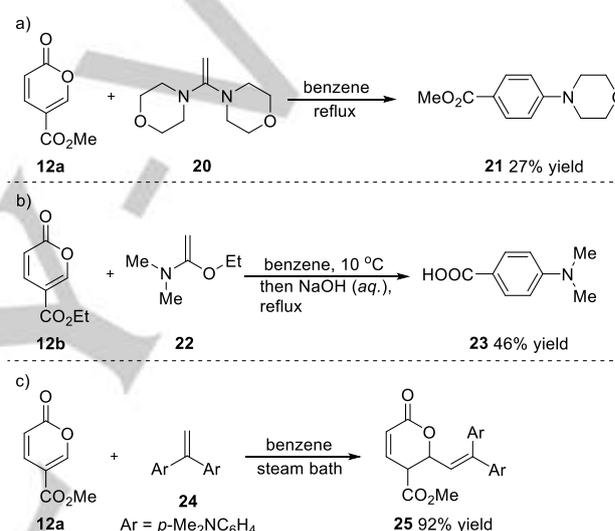
As mentioned above, 3-substituted and 5-substituted 2-pyrones are more reactive than 4-substituted and 6-substituted 2-pyrones for IEDDA reactions because of the resonance stabilization of the reaction intermediates. The classes of 2-pyrone bearing a carbonyl group at different positions are discussed in the following subsections.

3.1.1. IEDDA reactions of 5-carbonyl-2-pyrones

The first example of IEDDA reactions of 2-pyrones was reported by Behringer and co-worker in 1969, employing methyl or ethyl coumalate to react with various electron-rich dienophiles.^[10] When 1,1-dialkoxyethenes **13a** and **13b** were used as dienophiles, these reactions afforded bridged bicyclic compounds **14** exclusively in good yields and without the detection of regioisomer **15** (Scheme 7a). Similar results were observed between dienes **12** and ethyl vinyl ether **16a**, but cycloadducts **18** were thermally unstable at 160 °C and performed *retro*-DA reactions to give cyclohexadienes **19** which was followed by cycloadditions with another equivalent of ethyl vinyl ether **16a** to give 1:2-adducts **17**. The authors failed to characterize the exact position of the second ethoxy group of **17** because of the lack of high-resolution NMR technology (Scheme 7b). Further exploration of other substrates did not provide expected bicyclic products. For example, 1,1-dimorpholinoethylene **20** and 1-dimethylamino-1-ethoxyethylene **22** reacted with 2-pyrones to give corresponding aromatic compounds **21** and **23** (Scheme 8a and 8b). Likewise, increasing the electron density and steric hindrance of the pyrone ring also accelerated the conversion of bicyclic adducts to aromatic compounds. Interestingly, boiling methyl coumalate **12a** and N, N-dimethyl-4-vinylaniline **24** in benzene furnished adduct **25** which was considered as the positive evidence for stepwise mechanism (Scheme 8c).



Scheme 7. Thermal IEDDA reactions of methyl or ethyl coumalate with alkoxyethenes.

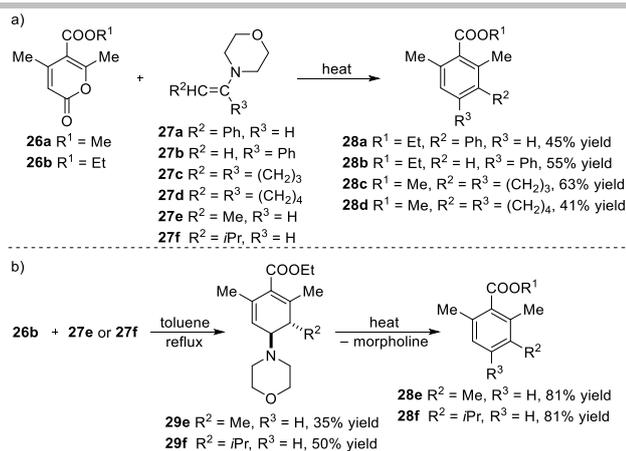


Scheme 8. Thermal IEDDA reactions of methyl or ethyl coumalate with substituted alkenes.

Like ethyl vinyl ether, morpholine enamines are suitable dienophiles for IEDDA reactions to access polysubstituted aromatic compounds. In 1983, Van Saun and co-workers investigated the regioselectivity of IEDDA reactions of 2-pyrones with morpholine enamines.^[11] Under thermal conditions, 2-pyrones **26** underwent IEDDA reactions with substituted morpholine enamines **27** followed by CO₂ extrusion *via retro*-DA reactions and aromatization *via* morpholine eliminations, preparing a series of highly functionalized benzoates **28** with complete regioselectivity (Scheme 9a). In two cases, cyclohexadiene intermediates **29** could be isolated and characterized, and further transformed into benzoates upon thermolysis (Scheme 9b).

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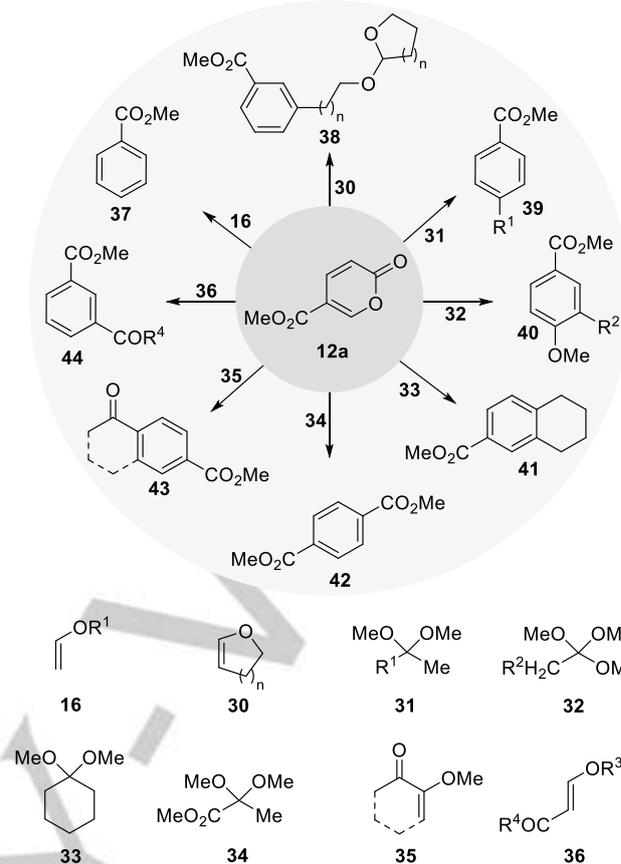
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Scheme 9. Regiospecific thermal IEDDA reactions of 2-pyrone with morpholine enamines.

Cycloadditions of 2-pyrone provides a renewable access to highly functionalized aromatic compounds primarily derived from diminishing petroleum-based sources. Indeed, methyl coumalate is easily obtained by dimerization of malic acid, which is produced by glucose fermentation. Kraus and co-workers have explored various dienophiles to react with methyl coumalate **12a** for sustainable access to substituted benzoates,^[12] and to find milder conditions for the conversion of malic acid into coumalic acid.^[13] Several vinyl ethers, ketals, and orthoesters were tested, as shown in Scheme 10. In 2013, Kraus and co-worker investigated the cycloadditions of methyl coumalate **12a** with cyclic vinyl ethers **30** or masked vinyl ethers, such as ketals (**31**, **33**) and orthoesters (**32**), under thermal conditions.^[12a] These transformations occurred in a domino sequence involving IEDDA reaction/CO₂ evolution/alcohol elimination to afford a great number of aromatic compounds.

In the plastic industry, dimethyl terephthalate (DMT, **42**) is commonly used for large-scale preparation of bis(2-hydroxyethyl) terephthalate (BHET), a monomer for producing polyethylene terephthalate (PET) which is the most common thermoplastic polymer in our daily life. In 2014, a renewable route for accessing DMT by using an IEDDA reaction of methyl coumalate **12a** with captodative ketal **34** was disclosed by Kraus and co-worker.^[12b] This protocol represents an alternative for reducing the dependence on petroleum products.

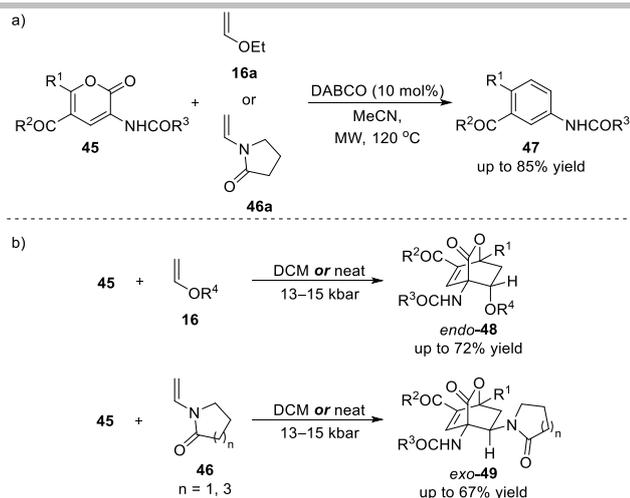


Scheme 10. Thermal cycloadditions of methyl coumalate with vinyl ethers, ketals, and orthoesters.

Conventional conditions (thermal and high pressure-promoted) for IEDDA reactions to access aromatic compounds always involve either high temperature (up to 220 °C) or long reaction time (up to 10 days). Microwave irradiation provides a solution to these drawbacks. Kočevar and co-workers reported microwave-assisted IEDDA reactions of 2-pyrone derivatives **45** with ethyl vinyl ether **16a** and enamine **46a** to rapidly afford substituted anilines **47** (Scheme 11a).^[14] A catalytic amount of DABCO played an important role for this transformation. Control experiments indicated that DABCO could facilitate the aromatization step instead of the cycloaddition or the CO₂ extrusion. Bicyclic adducts *endo*-**48** and *exo*-**49** were prepared by cycloadditions of 2-pyrone derivatives **45** with vinyl ethers **16** and enamines **46** under high pressure, in which no difference was observed between the results with or without the addition of DABCO (Scheme 11b), indicating that DABCO did not influence the cycloaddition step.^[14b] Moreover, exposure of the resulting bridged bicyclic lactone to microwave irradiation without DABCO resulted in a mixture of cyclohexadiene and aromatic compound with a ratio of 7:1, whereas with the addition of DABCO under otherwise identical reaction conditions the bridged bicyclic lactone was fully converted into corresponding aromatic compound.

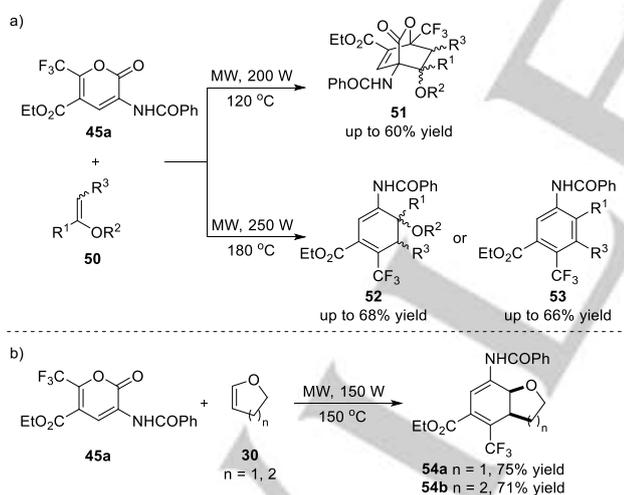
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Scheme 11. Comparison of microwave-assisted and high pressure-promoted IEDDA reactions of 2-pyrone.

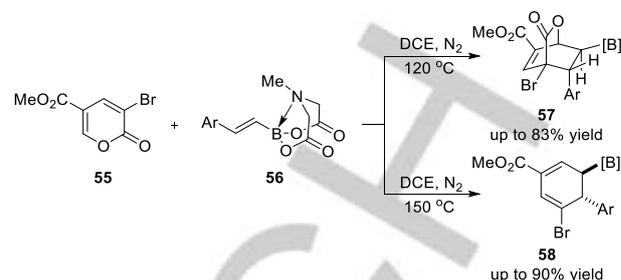
Attracted by the relevance of the trifluoromethyl group for bioactive molecules, Haufe and co-workers developed microwave-induced IEDDA reactions of 5-ethoxycarbonyl-2-pyrone **45a** bearing a trifluoromethyl group at C-6 position with acyclic vinyl ethers **50**. By adjusting the reaction conditions, bridged bicyclic adducts **51**, cyclohexadienes **52** and aromatic compounds **53** were achieved rapidly (Scheme 12a).^[15] Later, the authors expanded the substrate scope to cyclic vinyl ethers **30**. These cyclic vinyl ethers underwent IEDDA reactions with **45a**, providing an access to substituted dihydrobenzofurans **54** in good yields (Scheme 12b).^[16]



Scheme 12. Microwave-induced IEDDA reactions of 2-pyrone with acyclic and cyclic vinyl ethers.

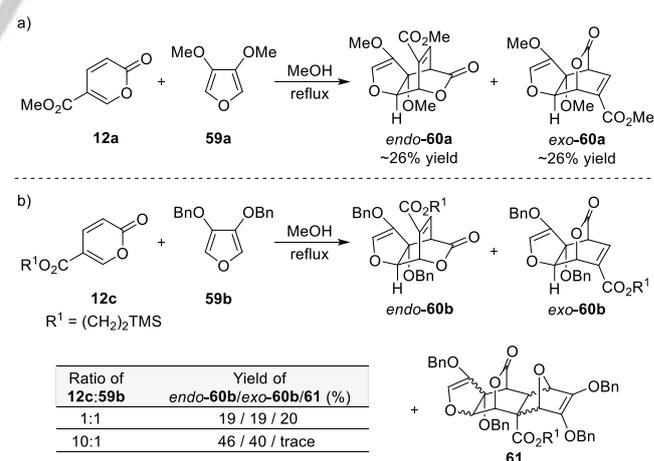
Organoboron compounds are of great importance in organic chemistry, and their synthesis and reactivity has attracted much attention. In 2019, Wang and co-workers discovered that alkenyl N-methyliminodiacetyl (MIDA) boronates **56** could serve as electron-rich dienophiles for IEDDA reactions. Alkenyl MIDA boronates **56** underwent IEDDA reactions with substituted 2-pyrone **55** at different temperatures, providing a series of bridged lactones **57** (when reacting at 120 °C) and

cyclohexadienylborons **58** (when reacting at 150 °C) with good regio- and diastereoselectivity (Scheme 13).^[17]



Scheme 13. IEDDA reactions of substituted 2-pyrone with alkenyl MIDA boronates.

Electron-rich heteroarenes, such as furans and indoles, with a masked moiety of O-substituted or N-substituted alkene, are good dienophiles for IEDDA reactions with 2-pyrone, in spite of the stability provided by the aromatic character. Jung and co-workers discovered in 1986 that alkyl coumalates **12** underwent [4+2] cycloadditions with 3,4-dialkoxyfurans **59** in an inverse-electron-demand fashion in which alkyl coumalates **12** acted as the electrophilic diene and the dialkoxyethene moiety of 3,4-dialkoxyfurans **59** acted as the dienophile, providing bridged lactones **60** with high regioselectivity (Scheme 14).^[18] For example, the IEDDA reaction between methyl coumalate **12a** and 3,4-dimethoxyfuran **59a** was carried out in boiling methanol for 2 hours to furnish 1:1-adducts **60a** as a 1:1 mixture of *endo/exo* isomers (Scheme 14a). It should be noted that the formation of 1:2-adduct **61** was observed when two analogous components **12c** and **59b** were used in an equimolar ratio for cycloaddition. By modifying the ratio of starting materials **12c** and **59b** to 10:1, this obstacle was overcome and only trace amount of 1:2-adduct **61** was detected (Scheme 14b).



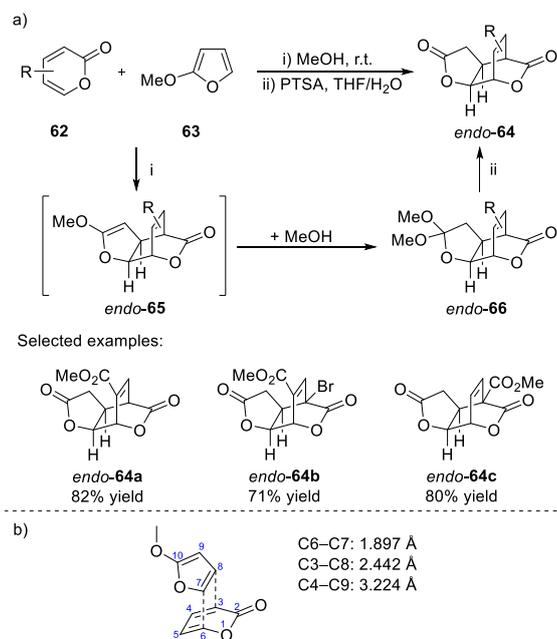
Scheme 14. IEDDA reactions of alkyl coumalates with 3,4-dialkoxyfurans.

In 2000, Liao and co-worker reported a similar strategy in which 2-methoxyfuran **63** acted as the dienophile (Scheme 15).^[19] Stirring the mixture of 2-pyrone **62** and 2-methoxyfuran **63** in methanol furnished bridged lactones *endo*-**65** which were not stable during purification by column chromatography.

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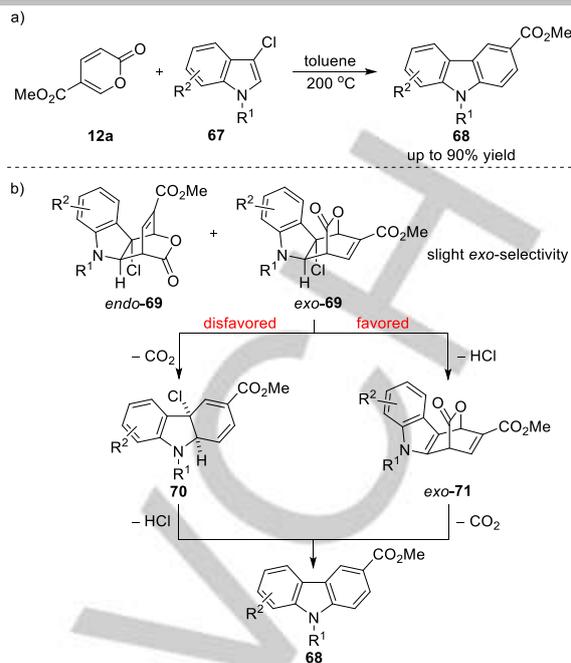
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Subsequent addition of methanol to the temporarily formed ketals *endo*-**65** afforded orthoesters *endo*-**66** which were further hydrolyzed into the corresponding dilactones *endo*-**64** by treatment with *p*-toluenesulfonic acid (Scheme 15a). Semiempirical calculations (AM1 and PM3) provided solid evidences to support the inverse-electron-demand pathway, in which the calculated distance between C6–C7 is shorter than that between C3–C8 (Scheme 15b).



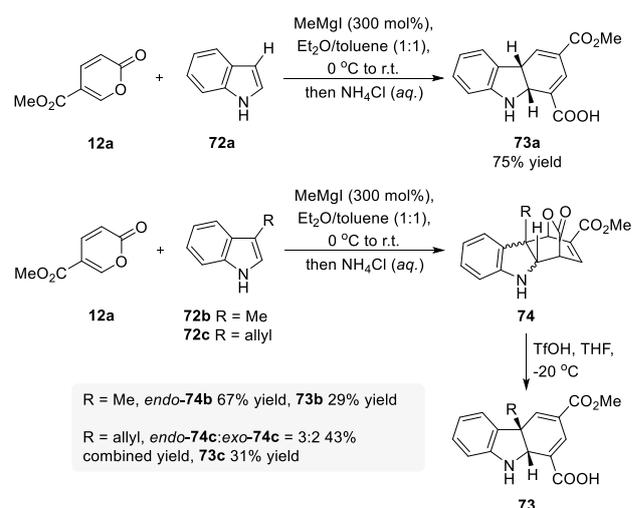
Scheme 15. IEDDA reactions of 2-pyrones with 2-methoxyfuran.

Substituted indoles **67** as dienophiles in IEDDA reactions with methyl coumalate **12a** for accessing highly functionalized carbazoles **68** were initially investigated by Kraus and co-workers in 2014 (Scheme 16a).^[20] This transformation involved a cascade sequence of IEDDA reaction/CO₂ extrusion/HCl elimination. To overcome the aromaticity of indoles, a good leaving group Cl was installed at C-3 position of indoles. Although IEDDA reaction step is kinetically and thermodynamically disfavored, the elimination of both HCl and CO₂ makes the IEDDA reaction step irreversible. In addition, the alkyl protecting group at N position played a key role in attenuating the decomposition of indoles under harsh conditions (up to 200 °C). In 2015, Domingo and co-workers used Density functional theory (DFT) calculations to illustrate the possible pathway in this methodology. DFT calculations suggested that the IEDDA reactions proceeded with slight *exo* stereoselectivity and the initial HCl elimination in the aromatization step was kinetically favored over the extrusion of CO₂ (Scheme 16b).^[21]



Scheme 16. IEDDA reactions of methyl coumalate with 1-alkyl-3-chloroindoles.

Recently, Kraus and co-worker found that indolemagnesium iodides, generated *in situ* from nonprotected indoles **72** with methylmagnesium iodide, reacted with methyl coumalate **12a** to access dihydrocarbazoles **73** in an inverse-electron-demand fashion (Scheme 17).^[22] When 3-alkylindoles **72b** and **72c** were used as dienophiles, bridged lactones **74** could be isolated and characterized, but both of them underwent *retro*-DA reactions at room temperature to give the starting materials. Under further treatment with trifluoromethanesulfonic acid, bridged lactones **74** were converted into dihydrocarbazoles **73** through lactone-opening reactions. Unfortunately, this strategy has a limited scope of substrates and affords dihydrocarbazoles in poor yields.



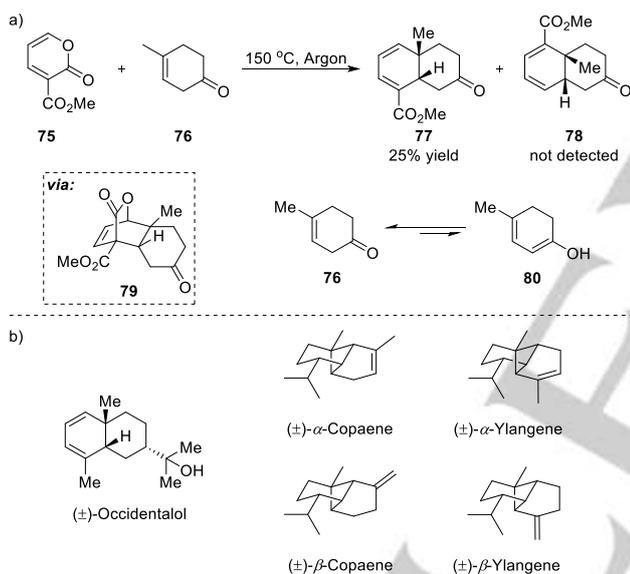
Scheme 17. IEDDA reactions of methyl coumalate with nonprotected indoles.

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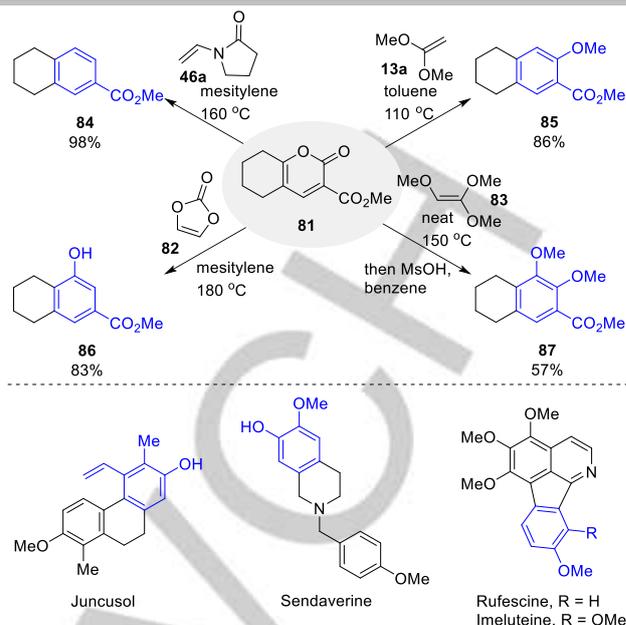
3.1.2. IEDDA reactions of 3-carbonyl-2-pyrone

3-Carbomethoxy-2-pyrone has been of great interest to synthetic chemists, although it has been less investigated than 5-carbomethoxy-2-pyrone. 3-Carbomethoxy-2-pyrone **75** is easily obtained by Knoevenagel reaction between a malonate derivative and 1,1,3,3-tetramethoxy propane, followed by acid-mediated cyclization. In 1972, Corey and co-worker developed a novel synthetic strategy involving a thermal IEDDA reaction of 3-carbomethoxy-2-pyrone **75** with 4-methyl-3-cyclohexenone **76** as a masked dienophile for accessing *cis*-fused bicyclo[4.4.0]decane **77** with complete regio- and stereocontrol.^[23] Regioisomer **78** was not detected in the resulting mixture. Other similar dienophiles, such as 4-substituted-1-methylcyclohexenes, but without β,γ -enone moiety all failed to undergo IEDDA reactions with 3-carbomethoxy-2-pyrone under similar conditions, indicating that electron-rich dienol **80**, generated *in situ* from β,γ -enone **76** via enolization, should be the reactive species in this reaction. The synthetic potential of this strategy was demonstrated by the total synthesis of sesquiterpenes (\pm)-occidentalol, (\pm)- α -copaene, (\pm)- α -ylangene, (\pm)- β -copaene and (\pm)- β -ylangene. (Scheme 18).



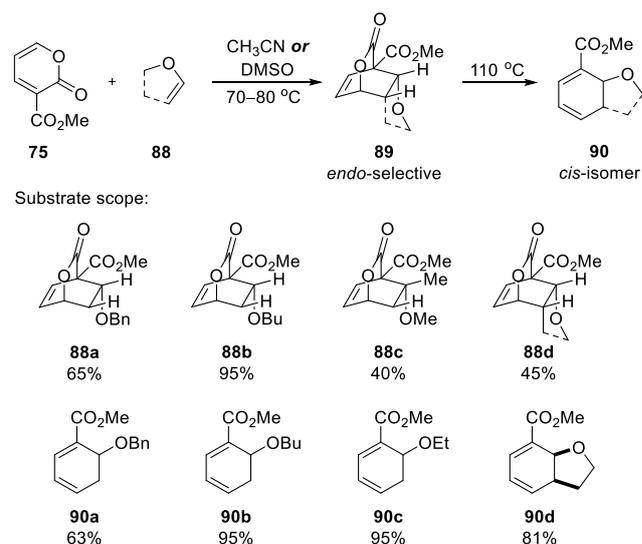
Scheme 18. IEDDA reaction of 3-carbomethoxy-2-pyrone with 4-methyl-3-cyclohexenone.

In the presence of a good leaving group on the dienophile, IEDDA reaction and CO₂ extrusion can be followed by elimination to afford aromatic compounds. This IEDDA reaction/CO₂ extrusion/aromatization sequence was deeply studied by Boger and co-worker, who disclosed successively that 3-carbomethoxy-2-pyrone derivative **81** could participate in IEDDA reactions with N-vinyl-2-pyrrolidinone **46a**, 1,1-dimethoxyethene **13a**, vinylene carbonate **82** and 1,1,2-trimethoxyethene **83** followed by CO₂ extrusion and aromatization to provide aromatic compounds **84–87** respectively.^[24] The synthetic value of these methods was demonstrated by the total synthesis of juncusol, sendaverine, rufescine and imeluteine (Scheme 19).



Scheme 19. IEDDA reaction/CO₂ extrusion/aromatization sequence with various dienophiles.

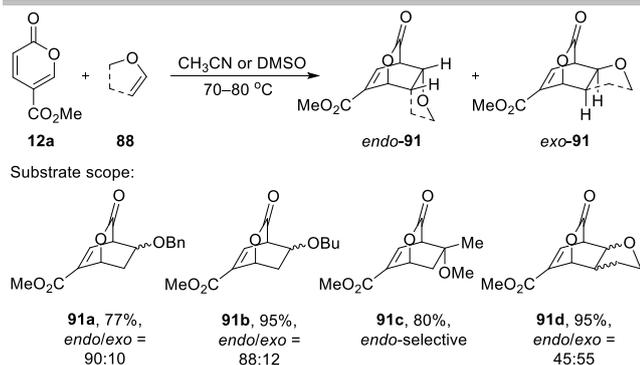
In 1993, Markó and co-workers reported an interesting comparison between the IEDDA reactions of 3-carbomethoxy-2-pyrone and 5-carbomethoxy-2-pyrone.^[25] The thermal IEDDA reactions of both of them with various vinyl ethers **88** proceeded smoothly at atmospheric pressure, leading to bridged bicyclic compounds **89** and **91**, respectively. It should be noted that IEDDA reactions of 3-carbomethoxy-2-pyrone **75** provided *endo*-specific bridged bicyclic compounds **89** (Scheme 20). This result is in sharp contrast with that of 5-carbomethoxy-2-pyrone **12a** which usually furnished a mixture of *endo* and *exo* isomers (Scheme 21). Moreover, heating the resulting bridged bicyclic compounds **89** in toluene at 110 °C afforded oxygenated cyclohexadienes **90** via CO₂ extrusion.



Scheme 20. Thermal IEDDA reactions of 3-carbomethoxy-2-pyrone with vinyl ethers.

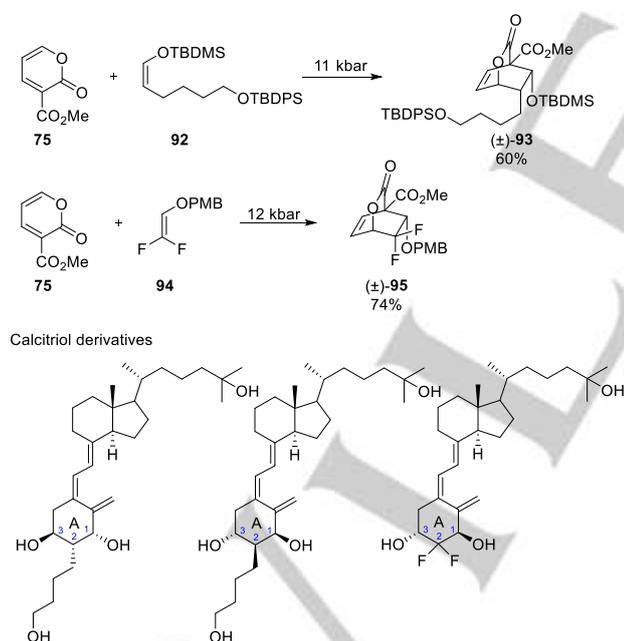
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Scheme 21. Thermal IEDDA reactions of 5-carbomethoxy-2-pyrone with vinyl ethers.

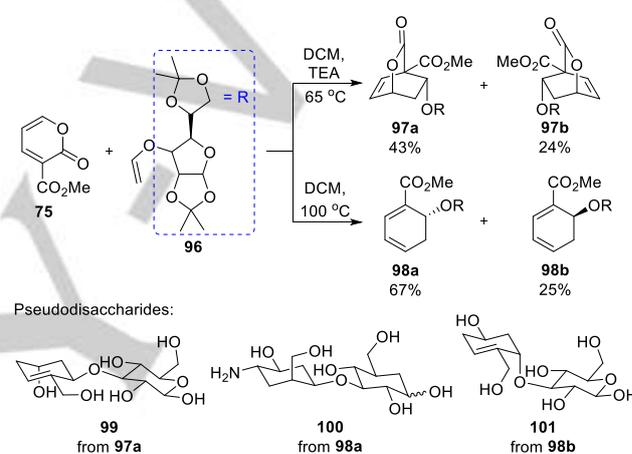
An interesting example of IEDDA cycloaddition of 2-pyrone involving an unconventional concerted mechanism was reported by Posner and co-workers. The authors studied the IEDDA cycloaddition reactions of 3-carbomethoxy-2-pyrone with 1,2-disubstituted alkenes. As described in Scheme 22, 3-carbomethoxy-2-pyrone **75** underwent high pressure-promoted IEDDA reactions with vinyl ethers **92** and **94** to provide racemic *endo*-**93** and *endo*-**95** as major products. The stereospecific obtention of *cis*-**93** was a proof that these reactions did not occur through the common stepwise mechanism, but rather in a concerted fashion. Further manipulation of these resulting bridged bicyclic lactones provided an access to a series of calcitriol derivatives.^[26]



Scheme 22. High pressure-promoted IEDDA reactions of 3-carbomethoxy-2-pyrone with vinyl ethers.

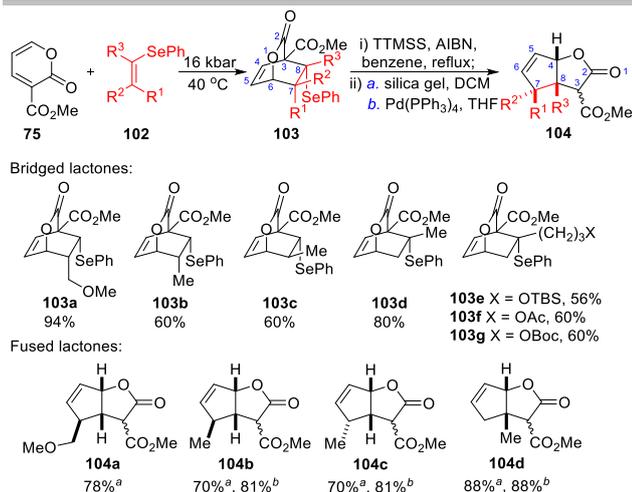
Oligosaccharides have many functions *in vivo*, including cell recognition and cell binding, which have been widely used in clinical medicine. Although a number of synthetic methods to access various oligosaccharides have been developed, the majority of those involved late-stage coupling between pseudo-

sugar and "true" sugar. To explore novel approaches for the synthesis of such pseudo-disaccharides, Afarinkia and co-workers targeted the application of IEDDA reactions of 3-carbomethoxy-2-pyrone to synthesize pseudo-sugars.^[27] As shown in Scheme 23, vinylated sugar **96** acting as an electron-rich dienophile participated in thermal IEDDA reactions with 3-carbomethoxy-2-pyrone **75**. By control of reaction temperature, the IEDDA reactions could provide bridged lactones (**97a** and **97b**) and cyclohexadienes (**98a** and **98b**), respectively. For example, when the reaction was carried out at 65 °C in the presence of triethylamine, bridged lactones **97a** and **97b** were obtained as diastereomers in 43% and 24% isolated yields, respectively. In contrast, heating the mixture of **75** and **96** at 100 °C afforded cyclohexadienes **98a** and **98b** in 67% and 25% isolated yields, respectively. Eventually, pseudodisaccharides **99–101** were achieved by further manipulation of these resulting cycloadducts.



Scheme 23. Application of IEDDA reactions of 3-carbomethoxy-2-pyrone to the synthesis of pseudodisaccharides.

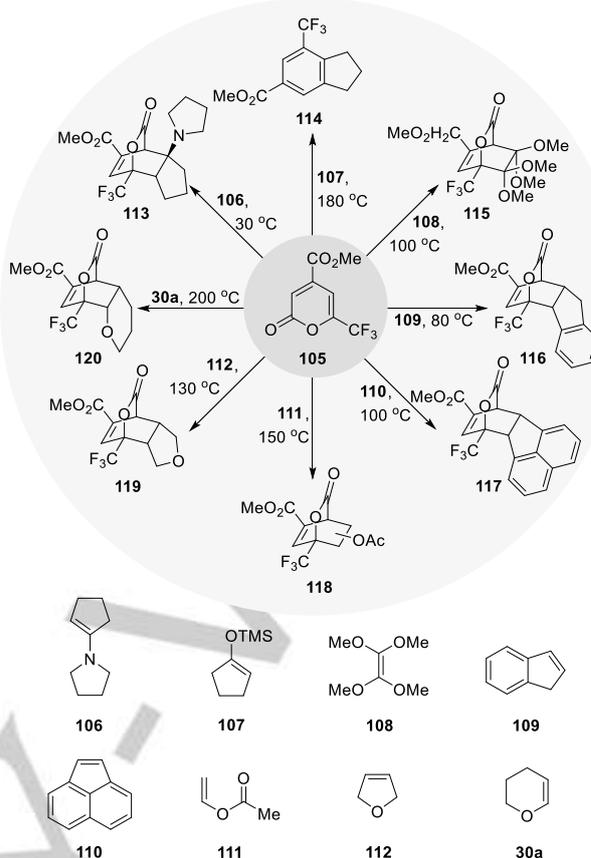
Owing to the similarity between selenium and oxygen, vinylselenides were also employed to react with 3-carbomethoxy-2-pyrone. This strategy was first achieved by Markó and co-workers, through high pressure-promoted IEDDA reactions of 3-carbomethoxy-2-pyrone **75** with various vinylselenides **102**, leading to bridged lactones **103** with complete regio- and *endo*-selectivity.^[28] It should be noted that the reaction was also diastereospecific, as (*Z*)-vinylselenide **102b** led to *cis*-substituted bridged lactone **103b**, while (*E*)-vinylselenide **102c** led to *trans*-substituted bicyclic lactone **103c**, in agreement with the concerted mechanism usually observed for high pressure-promoted IEDDA reactions. The resulting bridged lactones **103** could be readily converted into corresponding bicyclic fused lactones **104** by a two-step sequence of radical-mediated and acid-catalyzed (or palladium-catalyzed) skeletal rearrangements (Scheme 24).^[28,29]



Scheme 24. High pressure-promoted IEDDA reactions of 3-carbomethoxy-2-pyrone with vinylselenides.

3.1.3. IEDDA reactions of 4-carbonyl-2-pyrone

As mentioned above, the challenge of IEDDA reactions of 2-pyrone bearing an electron-withdrawing group at C-4 or C-6 position could be attributed to their relatively unstable reaction intermediates according to resonance stabilization. Furthermore, the lack of methods for preparations of 4-carbonyl-substituted and 6-carbonyl-substituted 2-pyrone deterred their use as electrophilic dienes for IEDDA reactions. In 1985, Martin and co-workers reported an efficient method for the synthesis of 4-methoxycarbonyl-2-pyrone **105** bearing a trifluoromethyl group at C-6 position. The novel 2-pyrone **105** could act as an electrophilic diene to participate in thermal IEDDA reactions with various alkenes including N-pyrrolidino-1-cyclopentene **106**, 1-trimethylsilyloxy-1-cyclopentene **107**, tetramethoxyethylene **108**, indene **109**, acenaphthylene **110**, vinylacetate **111**, 2,5-dihydrofuran **112**, 3,4-dihydro-2*H*-pyrane **30a**, from which most bridged lactones were obtained without extrusion of CO₂ (Scheme 25). It should be noted that electrophilic dienophiles, such as tetracyanoethylene and maleic anhydride, all failed to react with 2-pyrone **105**, indicating that these thermal [4+2] cycloadditions proceeded in an inverse-electron-demand fashion.^[30]



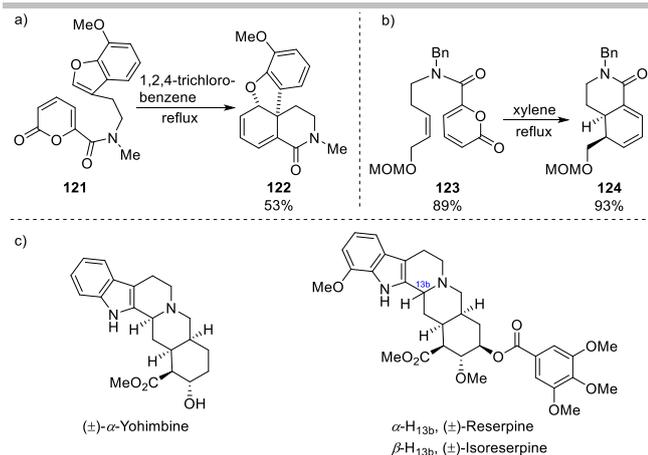
Scheme 25. Thermal cycloadditions of 4-methoxycarbonyl-2-pyrone with various alkenes.

3.1.4. IEDDA reactions of 6-carbonyl-2-pyrone

6-Substituted 2-pyrone are too unreactive to be attacked at C-6 position by intermolecular nucleophilic dienophiles because of electronic effects as well as steric hindrance caused by the C-6 substituent. However, this challenge could be overcome by intramolecular cycloadditions of 2-pyrone bearing a pendant alkene. This strategy was first reported by Ciganek in 1981, in which a thermal IEDDA reaction of 2-pyrone-6-carboxamide **121** with an intramolecular benzofuran was achieved and provided tetracyclic compound **122**, as depicted in Scheme 26a.^[31] Later, Martin and co-workers reported the total synthesis of indole alkaloids (±)-*α*-yohimbine, (±)-reserpine and (±)-isoreserpine by application of the similar strategy for the construction of essential functionalized hydroisoquinoline subunit.^[32]

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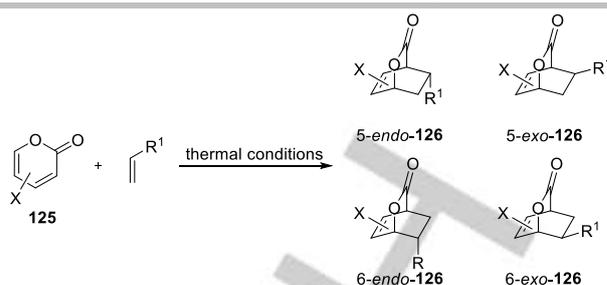
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Scheme 26. IEDDA reactions of 6-carbonyl-2-pyrones

3.2. IEDDA reactions of bromo-substituted 2-pyrones

The role of halogen substituents (Cl, Br, I) at different positions of 2-pyrone was investigated systematically by Afarinkia and co-workers in 2005.^[33] As shown in Scheme 27, cycloadditions of 2-pyrone bearing a bromine substituent at C-3, C-5 or C-4 position with various dienophiles were carried out under thermal conditions, leading to various bridged bicyclic lactones. Interestingly, 3-bromo-2-pyrone **125a** and 5-bromo-2-pyrone **125b**, both easily prepared by bromination and oxidation of 5,6-dihydro-2H-pyran-2-one, were ambiphilic and underwent both IEDDA reactions with electron-rich dienophiles and NEDDA cycloadditions with electron-poor dienophiles. In contrast, 4-bromo-2-pyrone **125c** preferred to participate in NEDDA cycloadditions with electron-poor dienophiles. Furthermore, in most cases, cycloadditions of 3-bromo-2-pyrone and 5-bromo-2-pyrone proceeded with good regio- and stereoselectivity favoring 5-*endo* cycloadducts predominantly, whereas those reactions of 4-bromo-2-pyrone proceeded with good stereoselectivity but without regioselectivity generating 5-*endo* and 6-*endo* cycloadducts in nearly 1:1 ratio. Similar results were also obtained by observing the cycloadditions of chloro-substituted 2-pyrones and iodo-substituted 2-pyrones. Moreover, the regio- and stereoselectivity of these reactions were rationalized by using density functional theory calculations.



Dienophiles	127	128	82	16b
125a	80% ^a 75/0/25/0 ^b	78% ^a 65/14/11/10 ^b	18% ^a 100/0 ^c	65% ^a 68/32/0/0 ^b
125b	94% ^a 65/15/20/0 ^b	96% ^a 40/42/11/7 ^b	43% ^a 80/20 ^c	81% ^a 72/28/0/0 ^b
125c	78% ^a 43/7/45/5 ^b	75% ^a 39/5/35/21 ^b	7% ^a 100/0 ^c	- -

^a Yields. ^b Ratios of isolated cycloadducts 5-*endo*/5-*exo*/6-*endo*/6-*exo*. ^c Ratios of mixed cycloadducts *endo*/*exo*.

Scheme 27. Thermal reactions of bromo-substituted 2-pyrones with various alkenes.

Although the efficiency and selectivity of these reactions are not significantly influenced by the nature of the halogen atom, bromo-substituted 2-pyrones have been more widely investigated than chloro- and iodo-substituted 2-pyrones in the past decades. There are two main factors accounting for this observation. Bromo-substituted 2-pyrones are more easily prepared than chloro- and iodo-substituted 2-pyrones. On the other hand, the late-stage reductive debromination of the resultant cycloadducts allows bromo-substituted 2-pyrones to be treated as the synthetic equivalent of 2-pyrone, the potential of which has been proved by a number of alkaloid total synthesis. The introduction of bromine atom could enhance the reactivity of 2-pyrones. Generally, the reactivity of bromo-substituted 2-pyrones would be as follows: 3,5-dibromo-2-pyrone > 5-bromo-2-pyrone > 3-bromo-2-pyrone, which will be discussed in the following subsections.

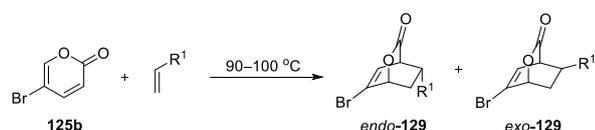
3.2.1. IEDDA reactions of 5-bromo-2-pyrones

Early investigations of the efficiency and stereoselectivity of dienophiles participating in IEDDA reactions with 5-bromo-2-pyrone were undertaken by Posner and Afarinkia.^[34] As outlined in Scheme 28, by adjusting the substituent of dienophiles, the IEDDA reactions proceeded with variable stereoselectivity and afforded either predominantly *endo* or predominantly *exo* cycloadducts. For example, vinyl ethers acted as nucleophilic dienophiles to react with 5-bromo-2-pyrone, mainly providing kinetically favored *endo* cycloadducts. Although *exo* cycloadducts were thermodynamically favored, these were not obtained at higher temperature because of further CO₂ extrusion.

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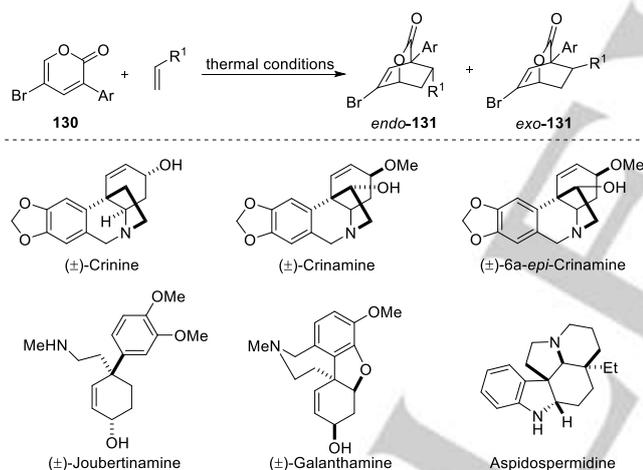
In contrast, cycloadditions of 5-bromo-2-pyrone with sterically hindered N-vinylpyrrolidinone and N-vinylphthalimide were highly *exo*-selective because secondary orbital interactions were prevented by steric hindrance.



R ¹	Yield	<i>endo/exo</i>	R ¹	Yield	<i>endo/exo</i>
OCH ₂ CH ₂ Cl	quant.	67/33	OCOMe	88%	30/70
OSiMePh ₂	47%	70/25	OCOPh	61%	50/50
N-Pyrrolidinone	79%	<10/90	OCHO	49%	40/60
NPhth	90%	<10/90			

Scheme 28. Thermal IEDDA reactions of 5-bromo-2-pyrone with electron-rich alkenes.

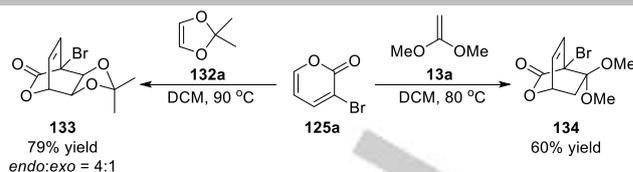
A similar strategy was also developed by Cho and co-workers in 2002, but 5-bromo-2-pyrone **130** bearing an aryl group at C-3 position was used as the electrophilic diene (Scheme 29).^[35] Later, the synthetic potential of this strategy was demonstrated by the total synthesis of (±)-joubertinamine,^[36] (±)-crinine,^[37] (±)-crinamine, (±)-6a-*epi*-crinamine,^[38] (±)-galanthamine^[39] and the core structure of aspidosperma alkaloid.^[40]



Scheme 29. Thermal IEDDA reactions of 5-bromo-3-aryl-2-pyrone with electron-rich alkenes.

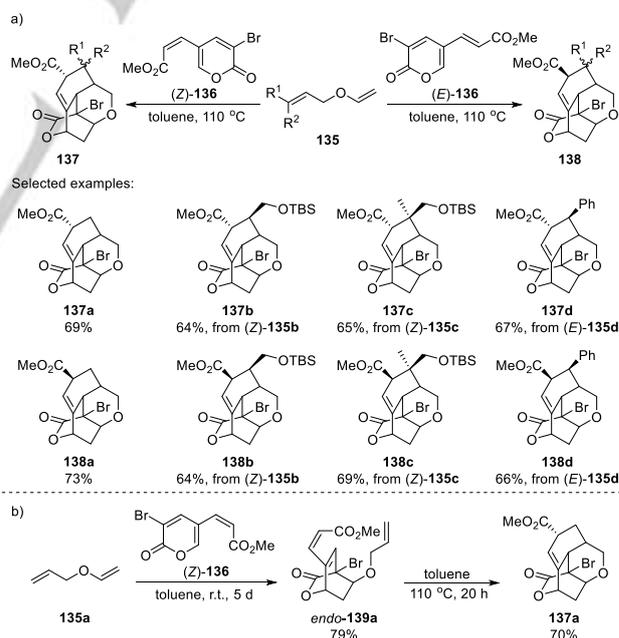
3.2.2. IEDDA reactions of 3-bromo-2-pyrones

Primary investigations on thermal IEDDA reactions of 3-bromo-2-pyrone with electron-rich dienophiles were carried out by Posner and co-workers in 1991. Through reaction of 3-bromo-2-pyrone **125a** with 2,2-dimethyl-1,3-dioxole **132a** and 1,1-dimethoxyethylene **13a** under thermal conditions, lactone **133** was obtained with good *endo*-selectivity, whereas lactone **134** was achieved with excellent regioselectivity, as shown in Scheme 30.^[41]



Scheme 30. Thermal IEDDA reactions of 3-bromo-2-pyrone with electron-rich dienophiles.

Tandem Diels–Alder reactions have attracted much synthetic attention in the past decades because of their powerful potential to rapidly increase molecular complexity in a single operation. In 2006, Cho and co-workers reported that 3-bromo-5-vinyl-2-pyrones underwent tandem Diels–Alder reactions with allyl vinyl ethers to prepare various novel tetracyclic lactones.^[42] Interestingly, the stereochemistry of the ester group in the reaction outcomes was only influenced by the configurations of acrylate fragment at C-5 position of 3-bromo-2-pyrones. For example, tandem Diels–Alder reactions of (*Z*)-**136** with **135** provided tetracyclic lactones **137**, whereas tandem Diels–Alder reactions of (*E*)-**136** with **135** afforded tetracyclic lactones **138**. Moreover, the configurations of the allyl group in dienophiles could not affect the stereocenters of resultant lactones (Scheme 31a). By running the reaction at room temperature, lactone *endo*-**139a** was isolated, which illustrates that the first step involves an IEDDA reaction. Heating the lactone *endo*-**139a** in toluene at 110 °C afforded the tetracyclic lactone **137a** (Scheme 31b).



Scheme 31. Tandem Diels–Alder reactions of 3-bromo-5-vinyl-2-pyrones with allyl vinyl ethers.

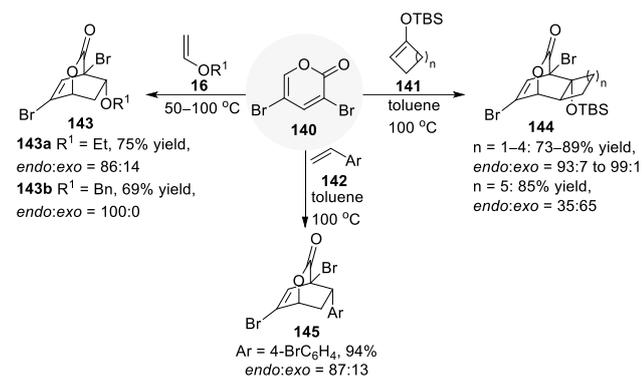
3.2.3. IEDDA reactions of 3,5-dibromo-2-pyrones

Compared with monobromo-substituted 2-pyrone, 3,5-dibromo-2-pyrone shows higher reactivity and better stereoselectivity in cycloadditions with both electron-rich and electron-poor dienophiles. Cho and co-workers have focused on the synthesis

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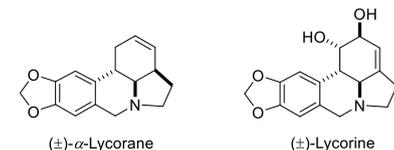
and transformation of this synthon for more than ten years. In 2001, they discovered an effective method to synthesize 3,5-dibromo-2-pyrone *via* bromo-decarboxylation of the corresponding carboxylic acid with NBS in one step.^[43] Later, thermal IEDDA reactions of 3,5-dibromo-2-pyrone with ethyl vinyl ether **16**, cycloalkenyl silyl ethers **141** and substituted styrenes **142** were carried out, providing bicyclic lactones **143–145** in good yields (Scheme 32).^[44] The synthetic potential of these strategies was demonstrated by the total synthesis of isocarbostyryl alkaloids^[45–47] and phenanthridine alkaloids.^[48,49]



Isocarbostyryl alkaloid



Phenanthridine alkaloid



Scheme 32. Thermal IEDDA reactions of 3,5-dibromo-2-pyrone with electron-rich dienophiles.

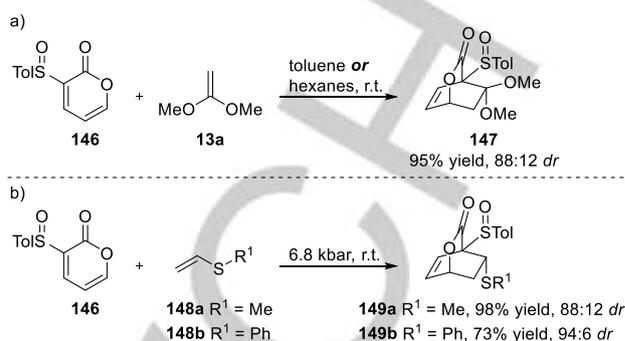
3.3. IEDDA reactions of sulfur-substituted 2-pyrones

Sulfur-substituted 2-pyrones, including 3-sulfinyl-2-pyrone and 3-sulfonyl-2-pyrone, are good cycloaddition partners for IEDDA reactions with electron-rich dienophiles. Because 3-sulfinyl-2-pyrone and especially 3-sulfonyl-2-pyrone are more electronically deficient than the corresponding 3-carbonyl-2-pyrone, their cycloadditions with vinyl ethers and vinyl thioethers could proceed under relatively mild reaction conditions so that the resultant bicyclic lactones could be isolated readily without CO₂ extrusion nor aromatization.

3.3.1. IEDDA reactions of 3-sulfonyl-2-pyrone

The first example of IEDDA reaction between 3-sulfonyl-2-pyrone **146** and 1,1-dimethoxyethylene **13a** was achieved by Posner and co-worker in 1985, leading to bicyclic lactone **147** in good yield (Scheme 33a). It should be noted that the stereogenic sulfonyl group induces a certain extent of diastereoselectivity, as the cycloadduct **147** was isolated as a mixture of two diastereomers (88:12 *dr*).^[50] Later, the same group broadened

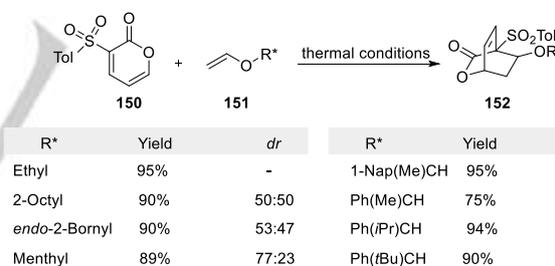
the substrate scope by using vinyl thioethers **148** as electron-rich dienophiles. These highly diastereoselective IEDDA reactions were promoted by high pressure at room temperature, as shown in Scheme 33b, providing bridged lactones **149**.^[51]



Scheme 33. IEDDA reactions of 3-sulfonyl-2-pyrone.

3.3.2. IEDDA reactions of 3-sulfonyl-2-pyrone

A number of optically active bridged bicyclic lactones **152** were prepared by Posner and co-worker in 1986 *via* substrate-based asymmetric induction, in which 3-sulfonyl-2-pyrone **150** underwent highly diastereoselective IEDDA reactions with several chiral vinyl ethers **151** (Scheme 34).^[52] These resulting bicyclic lactones could be used as chiral auxiliaries for efficient preparation of enantiopure polyfunctionalized cyclohexenes. The synthetic potential of this strategy was demonstrated by the total synthesis of (–)-methyl triacetyl-4-epishikimate.^[53]

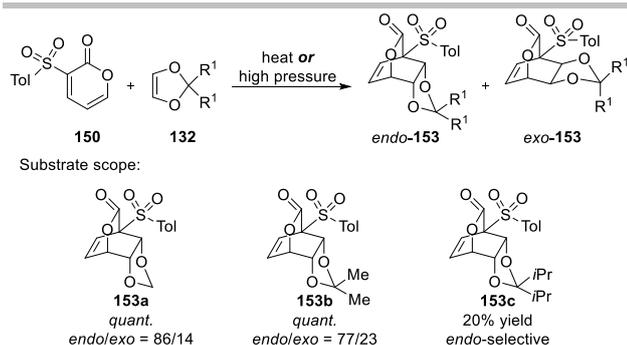


Scheme 34. IEDDA reactions of 3-sulfonyl-2-pyrone with chiral vinyl ethers.

In 1990, the same group reported the stereoselective IEDDA reactions of 3-sulfonyl-2-pyrone **150** with electron-rich 1,3-dioxoles **132** for accessing bicyclic lactones **153** (Scheme 35).^[54] These cycloadditions could be easily triggered by heating or high pressure. The reaction outcome was considerably influenced by the steric hindrance of dienophiles, in which more sterically hindered 1,3-dioxoles, such as 2,2-diisopropylidioxole, proved less reactive than unsubstituted 1,3-dioxole.

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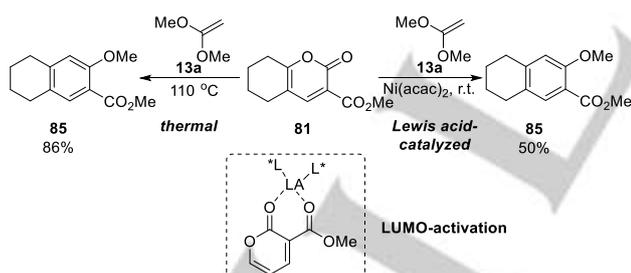


Scheme 35. IEDDA reactions of 3-sulfonyl-2-pyrone with 1,3-dioxoles.

4. Catalytic IEDDA reactions

4.1. Lewis acid-catalyzed IEDDA reactions of 2-pyrones

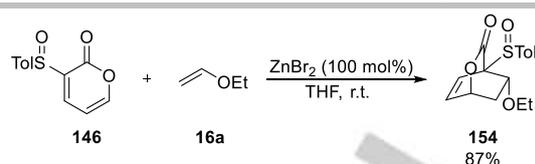
As mentioned above, the [2.2.2]-bicyclic lactones prepared from IEDDA reactions of 2-pyrones with dienophiles are usually so labile under thermal conditions that these reactions are plagued by CO₂ extrusion and subsequent aromatization. To avoid CO₂ extrusion from the initially formed cycloadducts, relatively mild reaction conditions were required to replace the previous harsh conditions. Since the first example of Lewis acid-catalyzed IEDDA reaction of 2-pyrone was discovered by Boger and co-worker in 1984, chemists have realized that Lewis acids are capable of catalyzing IEDDA reactions of 2-pyrones under mild conditions. In this report, only aromatic cycloadduct **85** was isolated in 50% yield when 5,6-disubstituted 3-carbomethoxy-2-pyrone **81** was treated with 1,1-dimethoxyethylene **13a** in the presence of catalytic Ni(acac)₂ at room temperature (Scheme 36).^[55] Generally, the role of Lewis acid in the mild catalytic IEDDA reaction is to lower the LUMO level of 2-pyrones. It should be noted that the addition of Lewis acid combining with chiral ligand allows to realize asymmetric variants of IEDDA reactions, which are impossible under non-catalytic conditions.



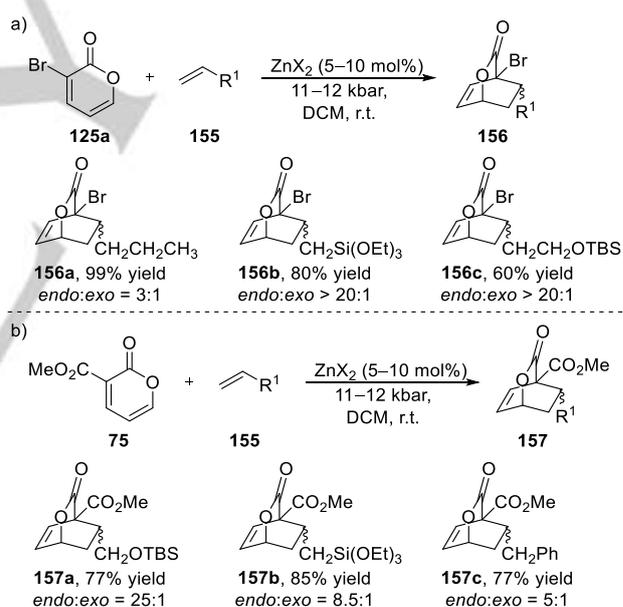
Scheme 36. Comparable results of thermal and Lewis acid-catalyzed IEDDA reactions.

4.1.1. Racemic IEDDA reactions of 2-pyrones

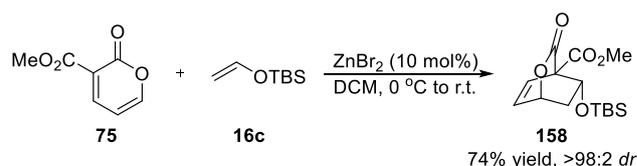
In 1987, Posner and co-workers reported that the IEDDA reaction of 3-sulfinyl-2-pyrone **146** with ethyl vinyl ether **16a** could be promoted by zinc bromide at room temperature, as shown in Scheme 37. The resulting bridged bicyclic lactone **154** was obtained in good yield. However, in this example stoichiometric amounts of zinc bromide were required.^[51]

Scheme 37. ZnBr₂-promoted IEDDA reaction of 3-sulfinyl-2-pyrone with ethyl vinyl ether.

Later, an improved version employing a combination of high pressure (11–12 kbar) and a catalytic amount of Lewis acid was developed by the same group, as outlined in Scheme 38. The reaction conditions promoted IEDDA reactions of 2-pyrones **125a** and **75** with several unactivated terminal alkenes **155**, leading to bridged bicyclic lactones **156** and **157** with good regioselectivities and stereoselectivities.^[56] Although the IEDDA reaction of more electron-rich silyl enol ether **16c** with 3-carbomethoxy-2-pyrone **75** could proceed easily in the presence of catalytic zinc salt (Scheme 39),^[57] various Lewis acids without high pressure failed to promote the IEDDA reactions of unactivated terminal alkenes, which indicates that the combination of Lewis acid with high pressure could provide a solution to enhance the reactivity of unactivated alkenes in IEDDA reactions with 2-pyrones.



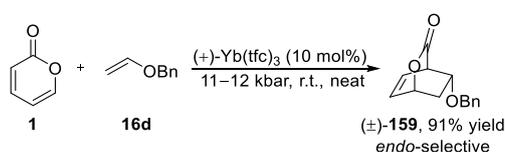
Scheme 38. Catalytic IEDDA reactions of 2-pyrones with unactivated terminal alkenes.

Scheme 39. ZnBr₂-catalyzed IEDDA reaction of 3-carbomethoxy-2-pyrone with silyl enol ether.

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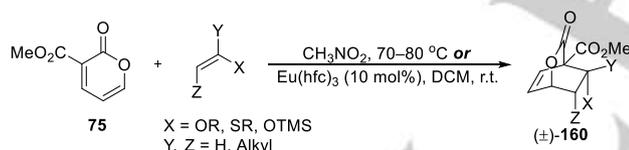
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Lanthanide are efficient catalysts for IEDDA reactions of 3-carbomethoxy-2-pyrone with a great number of electron-rich dienophiles. In 1994, Posner and co-worker reported an efficient IEDDA reaction of unsubstituted 2-pyrone **1** with electron-rich benzyl vinyl ether **16d** under a combination of high pressure (11–12 kbar) and a catalytic amount of (+)-Yb(tfc)₃, allowing to furnish racemic bridged bicyclic lactone **159** with complete regioselectivity and diastereoselectivity (Scheme 40).^[58] Control experiments illustrated the importance of the reaction conditions in the transformation. Undesired results occurred at atmospheric pressure under a catalytic amount of (+)-Yb(tfc)₃ or under high pressure without the catalyst. However, although chiral (+)-Yb(tfc)₃ was used as catalyst, no asymmetric induction was observed. This result was remarkable as it represents the first example of catalytic IEDDA reaction using unsubstituted 2-pyrones as diene.



Scheme 40. Yb(tfc)₃-catalyzed IEDDA reaction of 2-pyrone with benzyl vinyl ether.

In 1994, Markó and co-worker investigated the Eu(hfc)₃-catalyzed IEDDA reactions of 3-carbomethoxy-2-pyrone with electron-rich dienophiles by comparison with thermal IEDDA reactions.^[59] As shown in Scheme 41, a range of dienophiles proved to have lower reactivity and even no reactivity in thermal IEDDA reactions. However, in the presence of a catalytic amount of Eu(hfc)₃, the desired bridged bicyclic lactones **160** were obtained in good isolated yields.

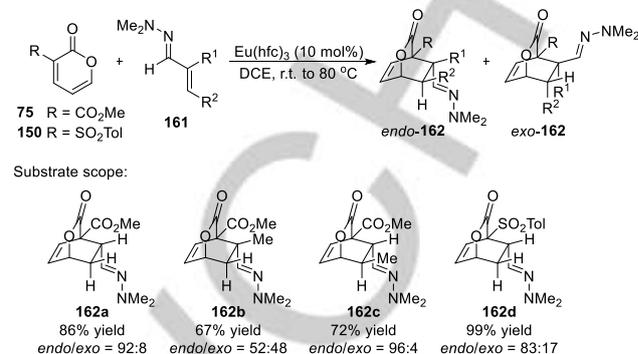


Entry	Dienophile	Yield	
		Thermal	Catalyzed
1		65%	88%
2		46%	56%
3		41%	96%
4		-	77%
5		-	67%
6		-	96%

Scheme 41. Comparable results of thermal and Eu(hfc)₃-catalyzed IEDDA reactions of 3-carbomethoxy-2-pyrone.

Transformation of α,β -unsaturated aldehydes to α,β -unsaturated hydrazones results in *umpolung*, for which the HOMO of the resulting α,β -unsaturated hydrazones could match with the LUMO of electron-poor 2-pyrones. In 2018, Tamura and co-

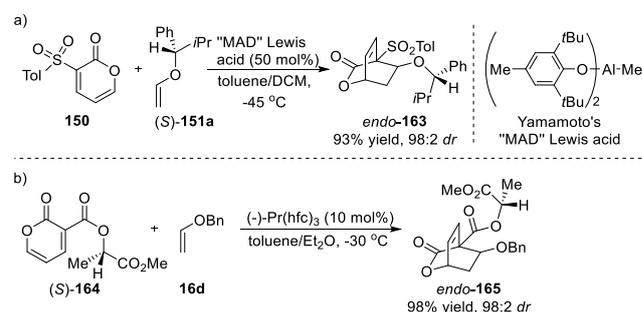
workers reported Eu(hfc)₃-catalyzed IEDDA reactions of 3-carbomethoxy-2-pyrone **75** and 3-sulfonyl-2-pyrone **150** with α,β -unsaturated hydrazones **161** for accessing bridged bicyclic lactones **162** (Scheme 42). In contrast, no cycloaddition occurred when acrolein was directly used as dienophile.^[60]



Scheme 42. Eu(hfc)₃-catalyzed IEDDA reactions of 2-pyrones with α,β -unsaturated hydrazones.

4.1.2. Diastereoselective IEDDA reactions of 2-pyrones using chiral auxiliaries

Installation of a chiral auxiliary on 2-pyrone or dienophile, prior to IEDDA reaction, provides a route to optically active bridged bicyclic lactones as separable diastereomeric mixtures. In 1990, Posner and co-workers used enantioenriched vinyl ether (S)-**151a** as dienophile for an aluminium-catalyzed IEDDA reaction with 3-sulfonyl-2-pyrone **150**, leading to chiral bridged bicyclic lactone *endo*-**163** as the major diastereomer in good isolated yield with excellent diastereoselectivity (Scheme 43a).^[61] Later, an alternative route to chiral bridged bicyclic lactones was achieved by the same group, in which 2-pyrone **164** bearing a chiral side chain at C-3 position was used as electrophilic diene in the catalytic IEDDA reaction with benzyl vinyl ether **16d** (Scheme 43b).^[62]



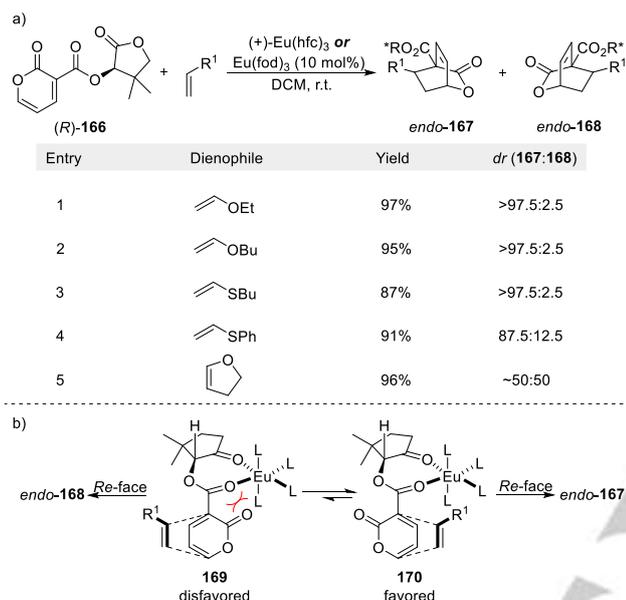
Scheme 43. Asymmetric IEDDA reactions by installation of a chiral auxiliary on 2-pyrone or dienophile.

In 1994, Markó and co-worker also investigated the catalytic IEDDA reactions of several chiral 3-carbonyl-2-pyrones and discovered that (*R*)-pantolactone auxiliary provided excellent yields and diastereoselectivities.^[63] Apart from dihydrofuran, other dienophiles reacted with (*R*)-**166** to deliver bridged bicyclic lactones *endo*-**167** as the major diastereomer with good to excellent diastereoselectivities (Scheme 44a). Remarkably, the

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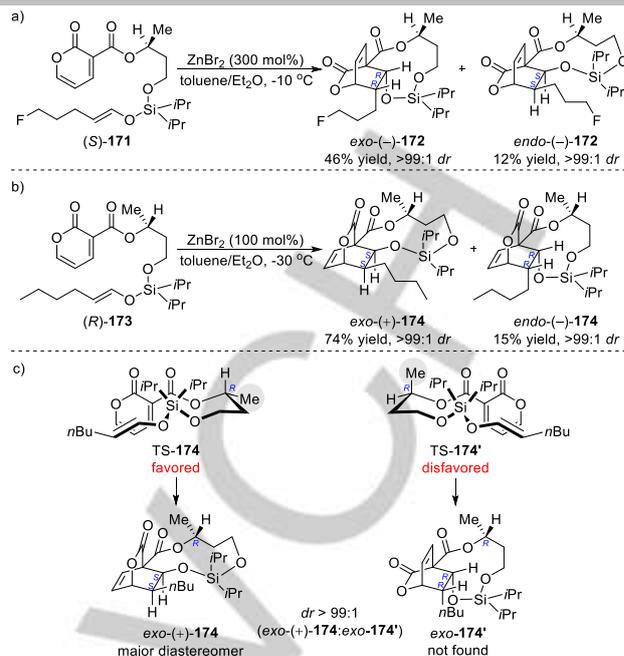
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major diastereomer possesses the opposite absolute configuration to that obtained by Posner *et al.* (*endo*-**165**, Scheme 43b), which could be rationalized by the chelated intermediates **169** and **170**. The rigidity of the seven-membered structure in **169** and **170** blocked the attack of dienophiles from *Si*-face because of the steric effect of α -methyl substituents. Moreover, the chelated intermediate **169** is disfavored because of the dipole-dipole repulsion between two carbonyl groups at the same side (Scheme 44b). No significant differences of diastereoselectivity were observed by using either achiral $\text{Eu}(\text{fod})_3$ or chiral (+)- $\text{Eu}(\text{hfc})_3$.



Scheme 44. Asymmetric IEDDA reactions of chiral 3-carbonyl-2-pyrone with achiral dienophiles.

An intramolecular diastereoselective IEDDA reactions of 2-pyrone was explored by Posner and co-workers in 1995, as shown in Scheme 45.^[64] The chiral 1,3-butanediol auxiliaries acted as a linker between *trans*-silyl enol ethers and 2-pyrone-3-carboxylate. Intramolecular IEDDA reactions of such 2-pyrone (*S*)-**171** and (*R*)-**173** were promoted by zinc bromide and proceeded in a stepwise, asynchronous fashion to give optically active *cis*-bicyclic lactones exclusively with acceptable *exo/endo* ratios. Interestingly, both *exo* and *endo* cycloadducts were diastereomerically pure (>99:1 *dr*) which could be rationalized by the orientation of the methyl group in the transition state. For example, transition state **TS-174** with the methyl group in pseudo-equatorial position would be more stable than **TS-174'** with the methyl group in pseudo-axial position (Scheme 45c).^[65] The energy difference in the transition state resulted in the predominant formation of one diastereomer.



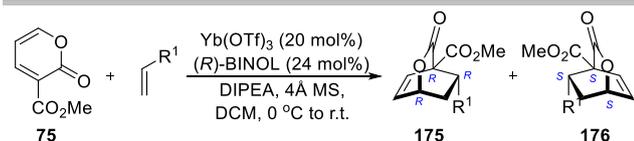
Scheme 45. Asymmetric intramolecular IEDDA reactions of chiral 2-pyrone.

4.1.3. Enantioselective IEDDA reactions of 2-pyrone

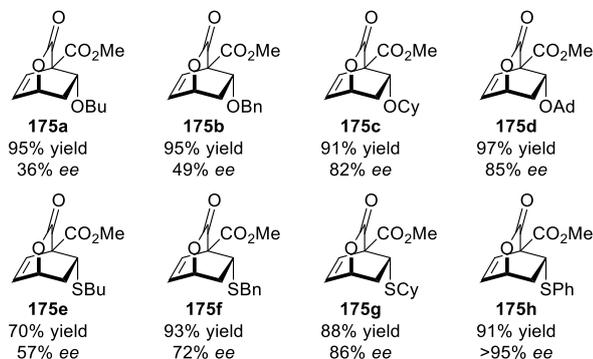
Highly diastereoselective, catalytic IEDDA reactions for preparation of chiral bridged bicyclic lactones can be achieved by using the auxiliary-based approach. However, this strategy is plagued by tedious preinstallation and removal of the chiral auxiliary. Therefore, direct asymmetric induction by chiral catalysis has attracted intensive research focus in the past decades. As mentioned, homochiral lanthanide shift reagents, such as $\text{Yb}(\text{tfc})_3$, $\text{Eu}(\text{hfc})_3$ and $\text{Pr}(\text{hfc})_3$, could not result in enantioselective synthesis without additional chiral ligands. The first example of catalytic enantioselective IEDDA reactions of 3-carbomethoxy-2-pyrone with *O*-substituted or *S*-substituted alkenes was realized by Markó and co-workers in 1994.^[66] Under catalysis by the combination of $\text{Yb}(\text{OTf})_3$ and (*R*)-BINOL, the reactions provided a great number of optically active bicyclic adducts **175** with variable enantioselectivities (Scheme 46). Interestingly, $\text{Yb}(\text{OTf})_3$ could not catalyze the cycloadditions between 3-carbomethoxy-2-pyrone and electron-rich alkenes, indicating that a more suitable enantioselective catalyst was formed by the combination of $\text{Yb}(\text{OTf})_3$ and (*R*)-BINOL. Later, the same group disclosed that the addition of THF, *t*BuOH or H_2O , in the absence of molecular sieves, led to dramatically improved enantioselectivities in several cases, although the role of the additive remains unclear.^[67]

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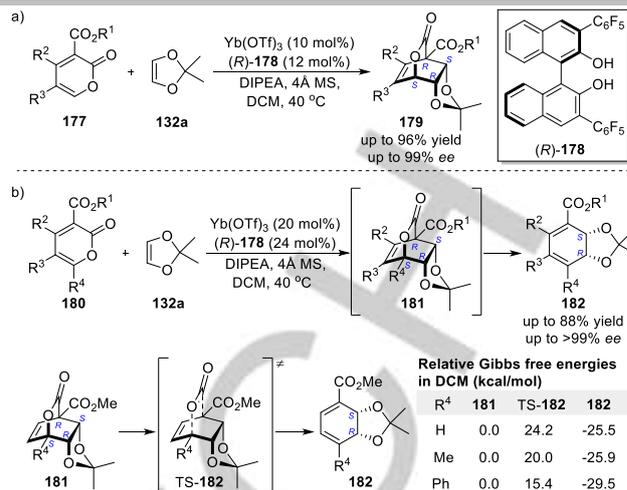


Selected examples:



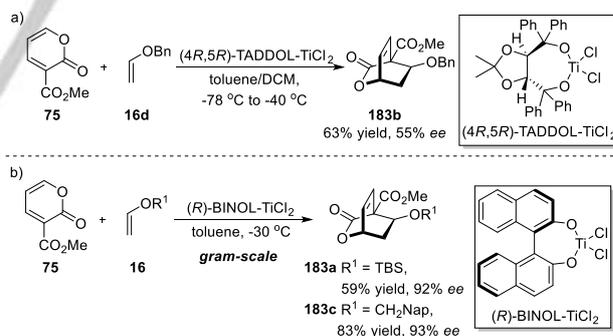
Scheme 46. Enantioselective IEDDA reactions of 3-carbomethoxy-2-pyrone with vinyl ethers.

More recently, an improved and efficient version of this strategy was achieved by Cai and co-workers, in which a series of bridged bicyclic lactones **179** and arene *cis*-dihydrodiols **182** were obtained in good yields with excellent enantioselectivities (Scheme 47).^[68] After extensive screening of chiral ligands in combination with Yb(OTf)₃, they found that the introduction of pentafluorophenyl groups on 3,3'-positions of (*R*)-BINOL resulted in dramatical increase of yield and ee value. Interestingly, with catalysis by the combination of Yb(OTf)₃ and chiral ligand (*R*)-**178**, the cycloadditions of 4,5-disubstituted-3-carboalkoxyl-2-pyrones **177** with 2,2-dimethyl-1,3-dioxole **132a** proceeded with almost complete enantioselectivities (Scheme 47a), whereas the cycloadditions of more encumbered 6-substituted-3-carboalkoxyl-2-pyrones **180** with 2,2-dimethyl-1,3-dioxole **132a** did not afford bridged bicyclic lactones **181** but directly generated arene *cis*-dihydrodiols **182** with excellent enantioselectivities (Scheme 47b). Both the congested scaffold of intermediates **TS-182** and the stabilization of C6-carbocation by substituents favored CO₂ extrusion under very mild conditions. Density functional theory calculations indicated that a lower energy barrier for CO₂ extrusion was observed when increasing the size of R⁴, in agreement with experimental results. The thermal CO₂ extrusion of bridged bicyclic lactones **179** generated from 4,5-disubstituted-3-carboalkoxyl-2-pyrones **177** had to be conducted in chlorobenzene with very low concentration to prevent dimerization of arene *cis*-dihydrodiols, leading to the isolation of arene *cis*-dihydrodiols in good yields without any erosion of ee values. This powerful method represents the first asymmetric chemical catalytic synthesis of arene *cis*-dihydrodiols and provides an efficient alternative to traditional enzymatic catalysis.



Scheme 47. Enantioselective IEDDA reactions of 3-carboalkoxyl-2-pyrones with 2,2-dimethyl-1,3-dioxole.

While Markó and co-workers studied enantioselective lanthanide catalysis, Posner and co-workers focused on chiral titanium complex-promoted enantioselective IEDDA reactions of 3-carbomethoxy-2-pyrone **75** with vinyl ethers **16**. As shown in Scheme 48, the combination of Ti(O*i*Pr)₂Cl₂ and chiral diol ligands could induce enantioselective IEDDA reactions. For example, under catalysis by stoichiometric (*4R,5R*)-TADDOL-TiCl₂ complex, the cycloaddition afforded optically active *endo*-adduct **183b**, albeit in moderate yield and enantioselectivity (Scheme 47a).^[69] Gratifyingly, after considerable condition optimization, highly enantioenriched bicyclic lactones **183a** and **183c** were obtained on gram scale with stoichiometric chiral (*R*)-BINOL-TiCl₂ complex (Scheme 48b).^[70]

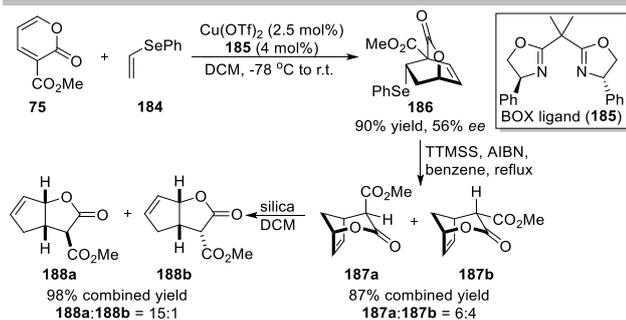


Scheme 48. Enantioselective IEDDA reactions of 3-carbomethoxy-2-pyrone promoted by chiral titanium complex.

In 2000, Markó and co-workers disclosed that the complex of copper(II) triflate and chiral bisoxazoline (BOX) ligand **185** was suitable for enantioselective catalytic IEDDA reaction of 3-carbomethoxy-2-pyrone **75** with vinylselenide **184**, affording corresponding bicyclic lactone **186** in good isolated yield but moderate enantiomeric excess (Scheme 49). The resulting bridged lactone **186** readily underwent late-stage radical-mediated and acid-catalyzed skeletal rearrangements to provide bicyclic fused lactones **188a** and **188b** with 15:1 ratio.^[71]

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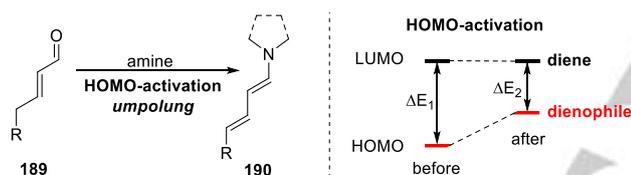
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Scheme 49. Enantioselective IEDDA reaction of 3-carbomethoxy-2-pyrone with vinylselenide.

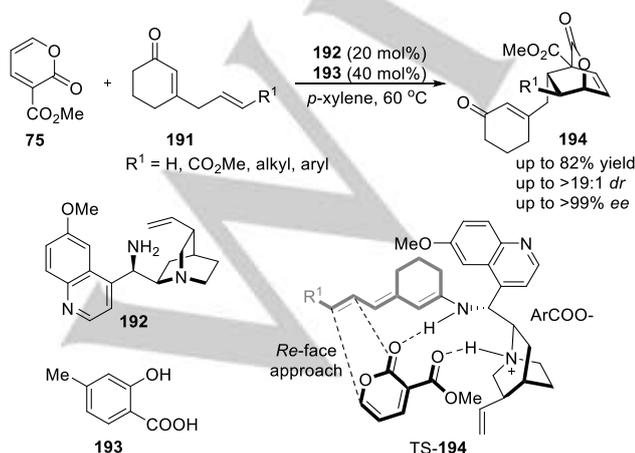
4.2. Organocatalytic IEDDA reactions of 2-pyrones

For decades, catalytic IEDDA reactions of 2-pyrones only relied on LUMO activation. Recently, chiral amine-catalyzed asymmetric IEDDA reaction of α,β -unsaturated carbonyl compounds based on HOMO-activation strategy has attracted considerable attention. As outlined in Scheme 50, the condensation of α,β -unsaturated carbonyl compounds **189** with chiral aminocatalysts would generate dienamines **190** which have proved to be excellent intermediates for IEDDA reactions.



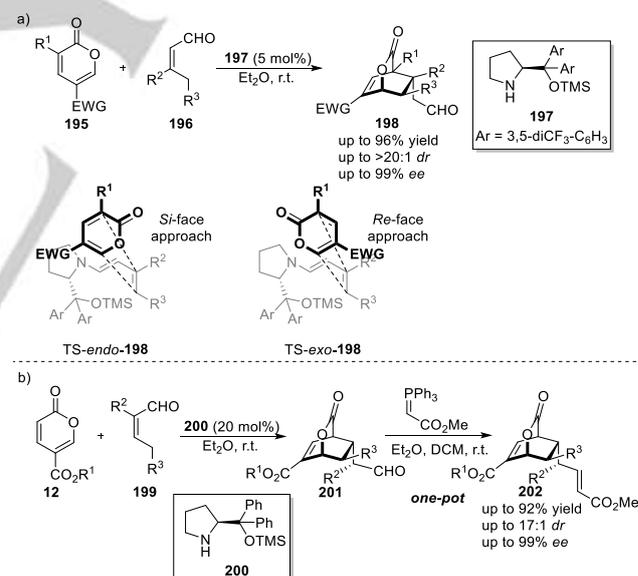
Scheme 50. HOMO-activation of α,β -unsaturated carbonyl compounds.

By using this strategy, Chen and co-workers reported in 2018 the first example of organocatalytic asymmetric IEDDA reactions of 3-carbomethoxy-2-pyrone **75** (Scheme 51). Under the catalysis of primary amine **192** derived from cinchona alkaloid, trienamine intermediates were generated *in situ* from cyclic 2,5-dienones **191**, the distal C–C double bond of which underwent cycloaddition with 3-carbomethoxy-2-pyrone **75** from *Re*-face approach, leading to a series of bicyclic lactones **194** in good yields and with excellent diastereo- and enantiocontrol.^[72]



Scheme 51. Organocatalytic asymmetric IEDDA reactions of 3-carbomethoxy-2-pyrone with cyclic 2,5-dienones.

Diarylprolinol silyl ethers have been widely used as chiral organocatalysts in enantioselective transformations of aldehydes. Recently, novel organocatalytic asymmetric IEDDA reactions of electron-poor 2-pyrones **195** and 3,3-disubstituted α,β -unsaturated aldehydes **196** were achieved by Snyder and co-workers.^[73] As shown in Scheme 52a, the cycloadditions between dienamine species, generated *in situ* from α,β -unsaturated aldehydes **196** by condensation with the aminocatalyst **197**, and electron-poor 2-pyrones **195** afforded an array of optically active bicyclic lactones **198** in moderate to good yields (46–96% yield) with variable stereoselectivities (1.1:1 *dr* to >20:1 *dr*, 21% *ee* to 99% *ee*). Because of secondary orbital overlap between 2-pyrones and trienamines in the transition state *TS-endo-198*, bicyclic lactones *endo-198* were obtained as major diastereomer in each case. It should be noted that the use of 3,3-disubstituted enals is essential to the isolation of desired products. Later, a similar strategy using 2,3-disubstituted α,β -unsaturated aldehydes **199** as dienophiles was developed by Albrecht and co-workers (Scheme 52b).^[74] However, the resulting bicyclic lactones **201** were not stable enough for purification. Further transformation of the cycloadducts **201** *via* Wittig reaction in one pot allowed to isolate a number of corresponding α,β -unsaturated esters **202** in good yields together with excellent diastereo- and enantioselectivities.



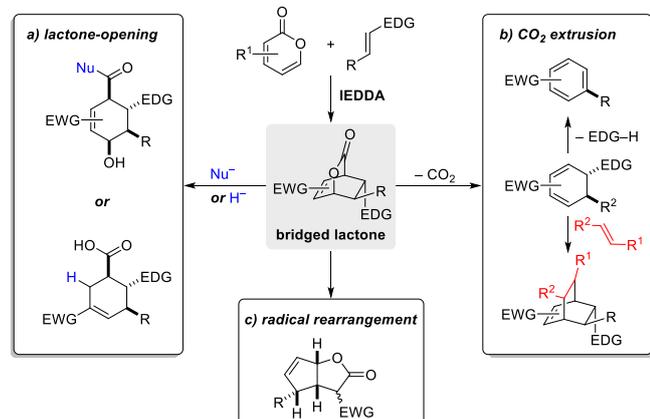
Scheme 52. Organocatalytic asymmetric IEDDA reactions of 2-pyrones with acyclic α,β -unsaturated aldehydes.

5. Applications in total synthesis

The IEDDA cycloaddition of 2-pyrone derivatives has found numerous applications in the total synthesis of natural products and drug candidates. This can be explained by the many possibilities for further functionalization of the [2.2.2]-bicyclic lactone. Firstly, the bridged lactones can be attacked by a nucleophilic reagent to furnish polysubstituted cyclohexenes (Scheme 53a). Secondly, CO₂ extrusion can readily happen

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upon thermolysis of the bridged lactones, leading to complex cyclohexadienes. Such 1,4-cyclohexadiene is a versatile synthon for further transformations, such as aromatization and cycloadditions (Scheme 53b). Finally, the bridged lactones can undergo radical skeletal rearrangements to deliver bicyclic fused lactones (Scheme 53c). In this section, we will discuss applications of the above IEDDA reactions in the total synthesis of natural products and drug candidates.

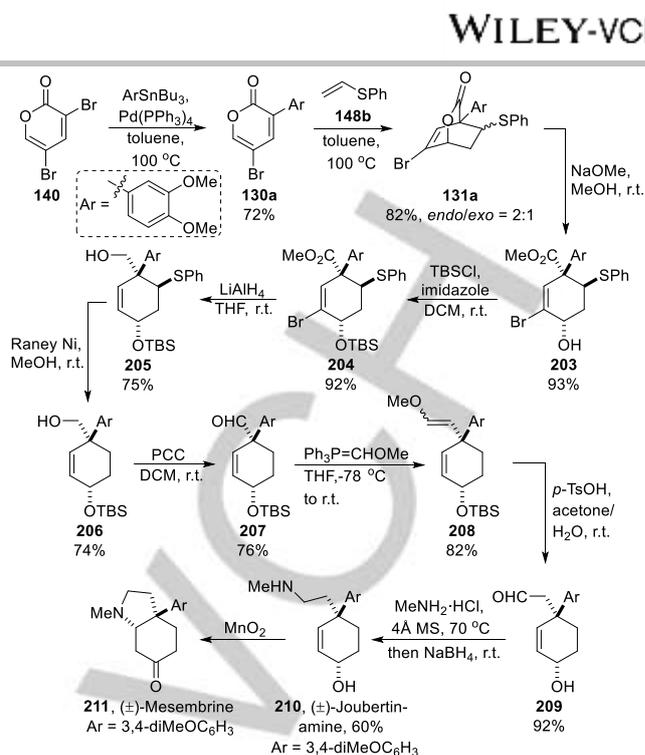


Scheme 53. Multiple characteristics of bridged lactones.

5.1. Ring-opening of the bridged lactones

5.1.1. Total synthesis of (±)-joubertinamine by Cho and co-worker

Joubertinamine is a seco-congener of *mesembrine* alkaloids which has proved potentially useful in the treatment of mental illnesses, such as depressive disorders. In 2007, Cho and co-worker reported a new efficient synthetic route to racemic joubertinamine in which the key cyclohexene fragment was introduced by a thermal IEDDA reaction of 5-bromo-3-aryl-2-pyrone **130a** prepared by a C3-selective Stille coupling between 3,5-dibromo-2-pyrone **140** and aryltin (Scheme 54).^[36] 5-Bromo-3-aryl-2-pyrone **130a** underwent the IEDDA reaction with vinyl sulfide **148b**, providing bridged lactone **131a** as a mixture of *endo/exo* isomers in 2:1 ratio. Ring-opening of lactone *endo*-**131a** and then protection of the resulting secondary alcohol **203** afforded ester **204**. Reduction of **204** was completed by treatment with LiAlH₄, which was accompanied by the removal of bromine atom to deliver sulfide **205**. Subsequent removal of thiophenyl group with Raney nickel generated alcohol **206**. PCC oxidation of the primary alcohol to aldehyde **207** followed by Wittig reaction provided vinyl ether **208** which was further treated with *p*-TsOH to furnish aldehyde **209**. The final conversion of **209** to (±)-joubertinamine **210** was accomplished by reductive amination with methylamine hydrochloride. According to a known procedure, (±)-joubertinamine could be easily converted into (±)-mesembrine **211** by oxidation in the presence of MnO₂.



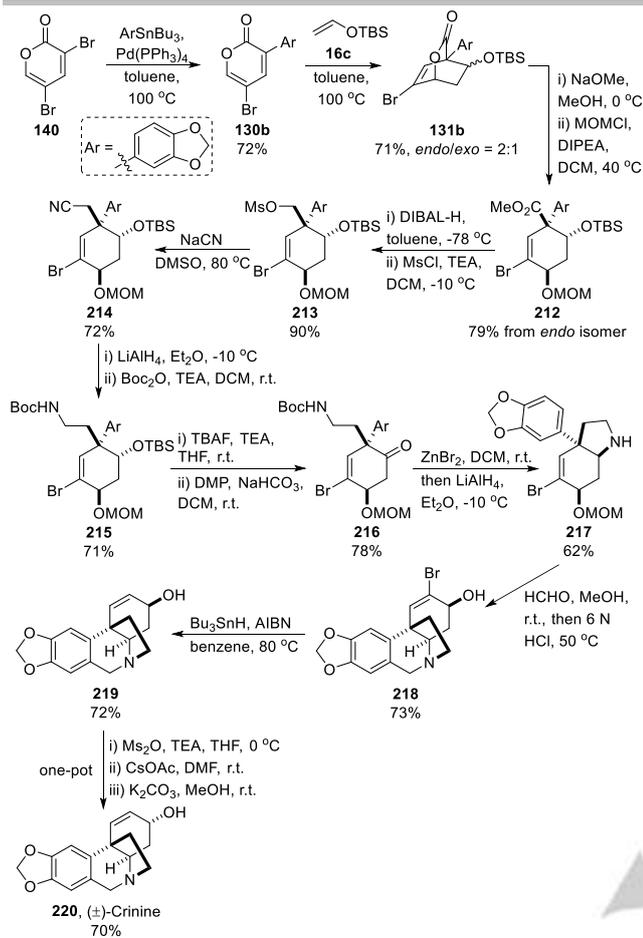
Scheme 54. Total synthesis of (±)-joubertinamine.

5.1.2. Total synthesis of (±)-crinine, (±)-crinamine and (±)-6a-*epi*-crinamine by Cho and co-workers

Crinane-type alkaloids, including crinine and crinamine, belonging to the family of *amaryllidaceae* natural products, have been of interest to organic chemists due to their potential antitumor activities. In 2008, Cho's group reported the total synthesis of (±)-crinine, (±)-6a-*epi*-crinamine and (±)-crinamine from cycloadduct **131b**. Similarly, bridged bicyclic lactone **131b** was achieved as a mixture of *endo/exo* isomers by a sequence of C3-selective Stille coupling reaction and IEDDA reaction, as illustrated in Scheme 55. Subsequent lactone opening and then protection of the resulting hydroxyl group as a MOM ether gave ester **212**. Reduction of **212** to the corresponding primary alcohol by excess DIBAL-H followed by mesylation provided mesylate **213**. Cyanation of **213** was followed by LiAlH₄ reduction of the resulting nitrile group and then Boc protection to deliver amine **215**. Selective deprotection of TBS-protected alcohol and subsequent oxidation by Dess–Martin periodinane furnished ketone **216**. Under treatment with ZnBr₂ in DCM, ketone **216** was converted into cyclic imine which was further reduced by LiAlH₄ to afford cyclic amine **217**. The bridged ring of **218** was assembled by a classical Pictet–Spengler reaction. Finally, reductive removal of bromine atom followed by inversion of the hydroxyl group furnished (±)-crinine **220**.^[37]

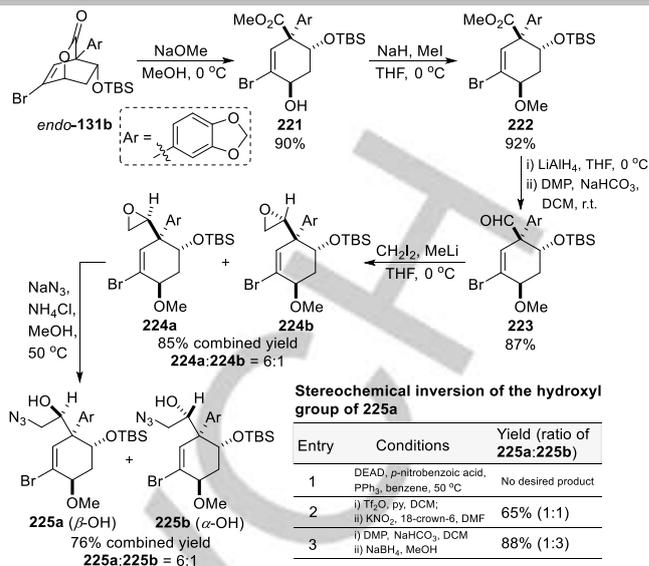
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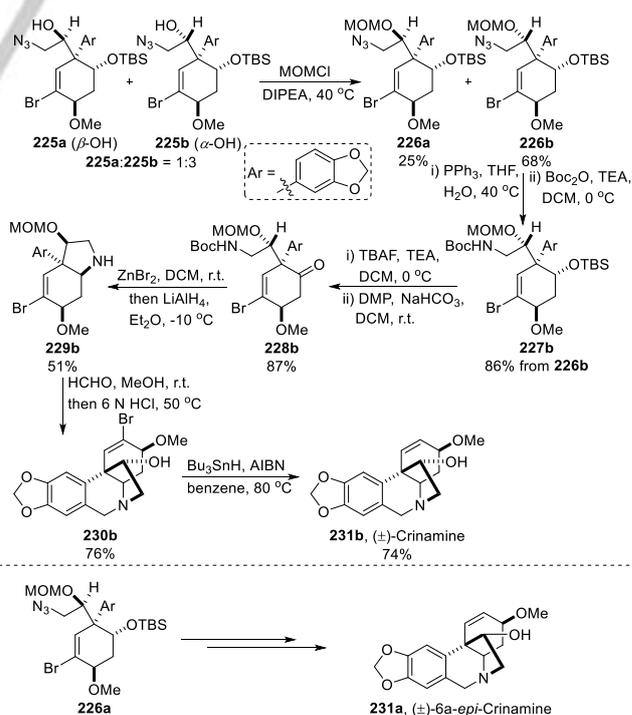


Scheme 55. Total synthesis of (±)-crinine.

Considering the structural similarity between crinine and crinamine, the authors attempted to install a hydroxyl group stereoselectively on the above intermediates by a sequence of epoxidation/epoxide opening.^[38] As illustrated in Scheme 56, this strategy commenced with ring-opening of lactone *endo*-131b and then protection of the resulting hydroxyl group as a methyl ether, leading to ester **222**. Reduction of **222** with LiAlH₄ to the corresponding primary alcohol followed by Dess–Martin oxidation afforded aldehyde **223**. Direct epoxidation of **223** with diiodomethane in the presence of lithium methoxide provided epoxides **224a** and **224b** as two inseparable diastereomers in 6:1 ratio. Subsequent epoxide opening by treatment with sodium azide allowed to access alcohols **225a** and **225b** as a diastereomeric mixture (**225a:225b** = 6:1). However, the authors failed to determine the relative stereochemistry of the major isomer **225a** at that time. Starting from alcohol **225a**, similar operations for the synthesis of (±)-crinine were carried out, allowing an access to (±)-6a-*epi*-crinamine **231a** (Scheme 57). Unfortunately, all attempts to epimerize the hydroxyl group at C-6a position of **231a** failed to provide (±)-crinamine **231b**. Therefore, the authors decided to use the minor isomer **225b** as the initial material. After investigating the epimerization of **225a**, the authors discovered that the diastereomeric ratio of **225a** and **225b** could be improved to 1:3 by an oxidation/reduction sequence (Entry 3).

Scheme 56. The synthesis of key intermediates of crinamine and 6a-*epi*-crinamine.

As outlined in Scheme 57, upon protection of alcohol **225a** and **225b** with MOMCl, two diastereomers **226a** and **226b** were isolated in 25% and 68% yields, respectively. Hydrolysis of azide **226b** with PPh₃/THF/H₂O followed by Boc protection afforded amine **227b** which was subjected to desilylation and subsequent oxidation to furnish ketone **228b**. Cyclization in the presence of ZnBr₂ provided an imine which was treated with LiAlH₄ to deliver **229b**. The key tetrahydroisoquinoline ring was constructed by a Pictet–Spengler reaction, leading to **230b**. The final conversion of **230b** to natural product (±)-crinamine **231b** was accomplished by reductive removal of the bromine atom.^[38]

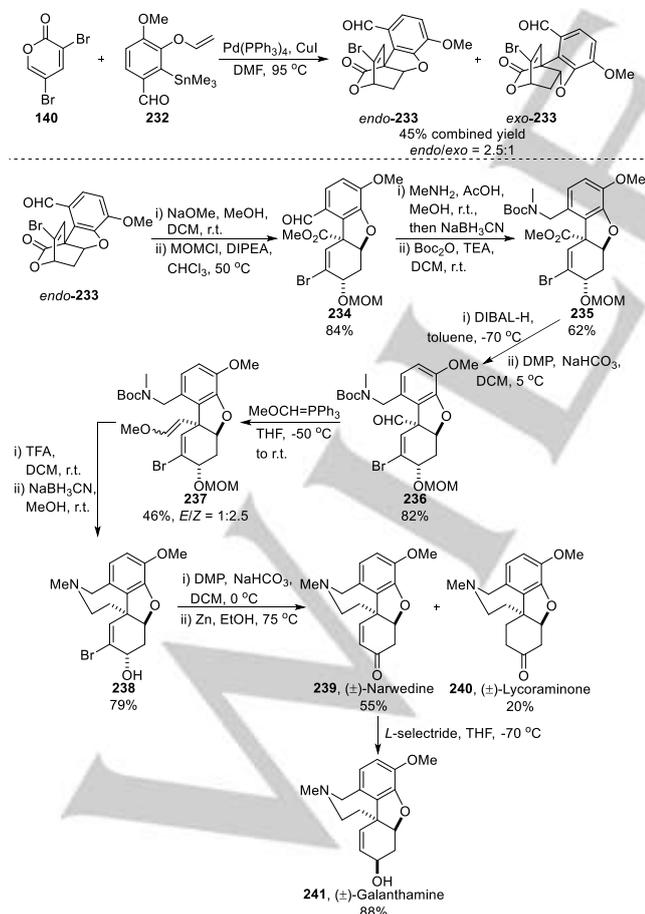
Scheme 57 The total synthesis of (±)-crinamine and (±)-6a-*epi*-crinamine.

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5.1.3. Total synthesis of (±)-narwedine, (±)-lycoraminone and (±)-galanthamine by Cho and co-workers

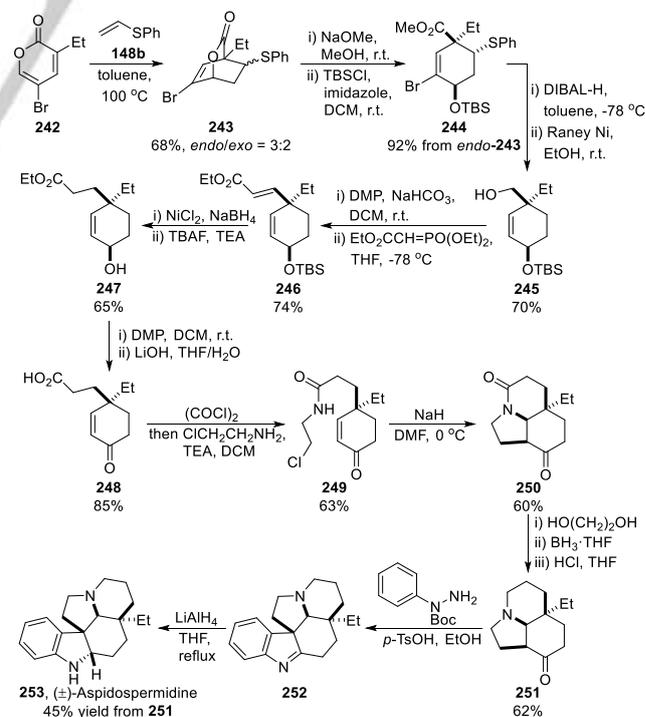
The intramolecular IEDDA reaction of 5-bromo-3-aryl-2-pyrone bearing a vinyl group on the aryl ring was investigated by Cho and co-workers, and used for the synthesis of (±)-narwedine, (±)-lycoraminone and (±)-galanthamine.^[39] Under thermal conditions, the regioselective Stille coupling of 3,5-dibromo-2-pyrone **140** with aryltin **232** allowed to furnish tetracyclic lactones *endo*-**233** and *exo*-**233** directly rather than the expected Stille coupling product. Lactone opening of *endo*-**233** followed by protection of the resulting hydroxyl group as a MOM ester afforded aldehyde **234**. Subsequent reductive amination of aldehyde **234** with methylamine provided a secondary amine which was then protected with a Boc group to give ester **235**. The ester **235** was converted into aldehyde **236** in a two-step manipulation involving reduction by DIBAL-H and Dess–Martin oxidation. By employing Wittig olefination with methoxymethyl phosphorus ylide, compound **237** was obtained as an enol ether which was subjected to acid-promoted hydrolysis in the presence of TFA and provided the corresponding aldehyde, along with removal of both Boc and MOM protecting groups. The resulting aldehyde underwent intramolecular reductive amination to construct cyclic amine **238**. Dess–Martin oxidation of **238** followed by Zn-promoted debromination afforded (±)-narwedine **239** and over-reduced product (±)-lycoraminone **240** in 55% and 20% yields, respectively. The final reduction of (±)-narwedine by *L*-selectride was accomplished and furnished (±)-galanthamine **241** which is a commercially available drug used for the treatment of Alzheimer's disease (Scheme 58).



Scheme 58. Total synthesis of (±)-narwedine, (±)-lycoraminone and (±)-galanthamine.

5.1.4. Total synthesis of (±)-aspidospermidine by Cho and co-workers

Aspidosperma alkaloid is one of largest groups of indole alkaloids, the common framework of which is a complicated pentacyclic structure. The total synthesis of (±)-aspidospermidine was completed by Cho's group in 2010, starting from an IEDDA reaction of 3-ethyl-5-bromo-2-pyrone **242** with vinyl sulfide **148b**.^[40] As shown in Scheme 59, the conversion of cycloadduct *endo*-**243** to the corresponding ester **244** was accomplished in a two-step operation including ring-opening of lactone and TBS-protection of the resulting hydroxyl group. Reduction of ester **244** to corresponding alcohol was followed by reductive removal of both bromine atom and phenylthio group with Raney nickel to furnish cyclohexene **245** which underwent Dess–Martin oxidation and then Wittig olefination to afford α,β -unsaturated ester **246**. The C–C double bond of ester **246** was reduced by NaBH₄ in the presence of NiCl₂. Subsequent desilylation, Dess–Martin oxidation and hydrolysis of the methyl ester were undertaken to furnish cyclohexenone **248**. Conversion of carboxylic acid to acyl chloride followed by reaction with 2-chloroethylamine provided amide **249**. Under treatment with sodium hydride, amide **249** was transformed into tricyclic amide **250** via a reaction sequence of conjugate addition and alkylation. A three-step manipulation involving selective protection, amide reduction and deprotection was carried out to convert amide **250** into cyclic amine **251**. Finally, the indoline fragment was introduced by Fischer indole synthesis and subsequent reduction by LiAlH₄ to complete the total synthesis of (±)-aspidospermidine **253**.



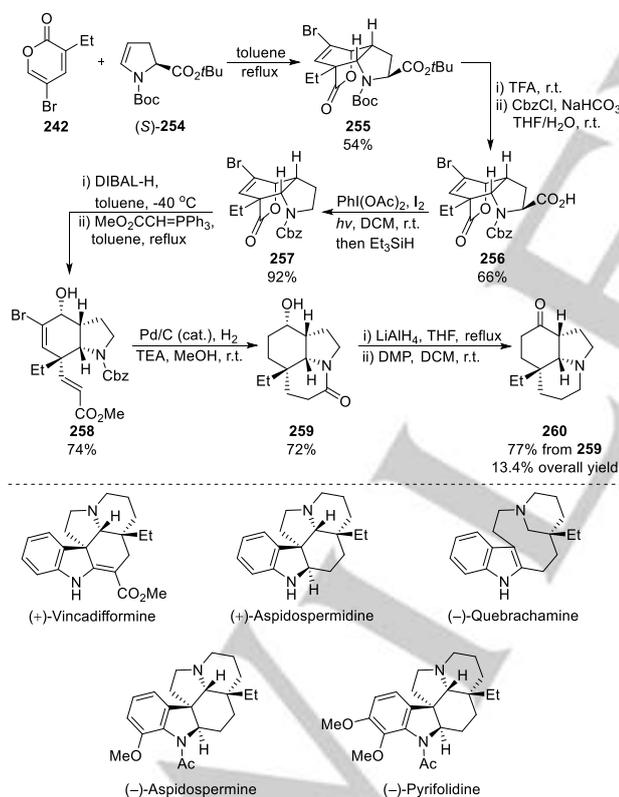
Scheme 59. Total synthesis of (±)-aspidospermidine.

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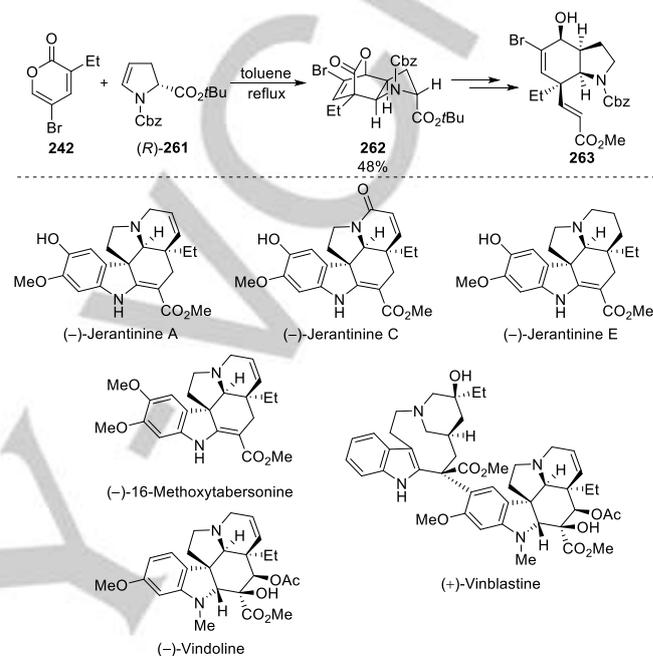
5.1.5. Total synthesis of *Aspidosperma* and *Vinca* alkaloids by Jiang and co-workers

In 2017, Jiang and co-workers reported an *exo*-selective IEDDA reaction of 3-ethyl-5-bromo-2-pyrone **242** with chiral pyrroline (*S*)-**254** for the enantioselective construction of a series of *Aspidosperma* alkaloids.^[75] As described in Scheme 60, highly functionalized lactone **255** was obtained as an *exo*-isomer by refluxing a mixture of 3-ethyl-5-bromo-2-pyrone **242** and chiral pyrroline (*S*)-**254** in toluene. The removal of Boc protecting group and hydrolysis of ester group were achieved in the presence of trifluoroacetic acid in a single step, followed by reprotection of the resultant secondary amine with CbzCl to provide carboxylic acid **256**. Decarboxylation of carboxylic acid **256** afforded lactone **257** which underwent DIBAL-H reduction and subsequent Wittig olefination to furnish hydroindole **258**. Then **258** was converted into tricyclic lactam **259** via a cascade process of Pd/C-catalyzed hydrogenation, deprotection and amidation. Reduction of **259** with LiAlH₄ and subsequent Dess–Martin oxidation completed the construction of tricyclic ketone **260** which is a key synthetic intermediate for the divergent synthesis of *Aspidosperma* alkaloids. By this concise strategy, the authors realized the total synthesis of 14 *Aspidosperma* alkaloids, such as (+)-vincadifformine, (+)-aspidospermidine, (-)-quebrachamine, (-)-aspidospermine, (-)-pyrifolidine.

Scheme 60. Total synthesis of *Aspidosperma* alkaloids.

Later, the same group applied a similar strategy to synthesize various oxygenated *Aspidosperma* and *Vinca* alkaloids.^[76] As shown in Scheme 61, the IEDDA cycloaddition reaction of 3-ethyl-5-bromo-2-pyrone **242** with chiral pyrroline (*R*)-**261** provided chiral bridged lactone **262** as an *exo*-isomer which

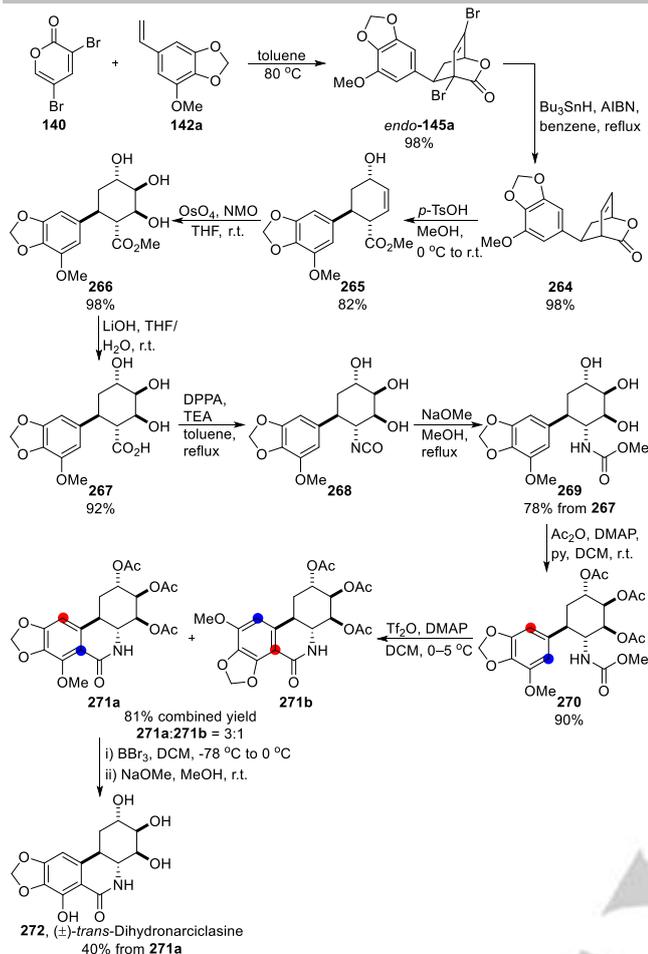
could be further transformed into highly functionalized hydroindole **263**, the key intermediate for the synthesis of oxygenated *Aspidosperma* and *Vinca* alkaloids. Finally, commercially available antitumor drugs (+)-vinblastine and five other oxygenated *Aspidosperma* alkaloids were accomplished concisely by the authors. This strategy demonstrates the feasibility of constructing enantiopure alkaloids by the stereocontrolled IEDDA reaction of 3-ethyl-5-bromo-2-pyrone with chiral pyrroline.

Scheme 61. Total synthesis of *Aspidosperma* and *Vinca* alkaloids.5.1.6. Total synthesis of (±)-*trans*-dihydronarciclasine, (±)-pancratistatin and (±)-1-*epi*-pancratistatin by Cho and co-workers

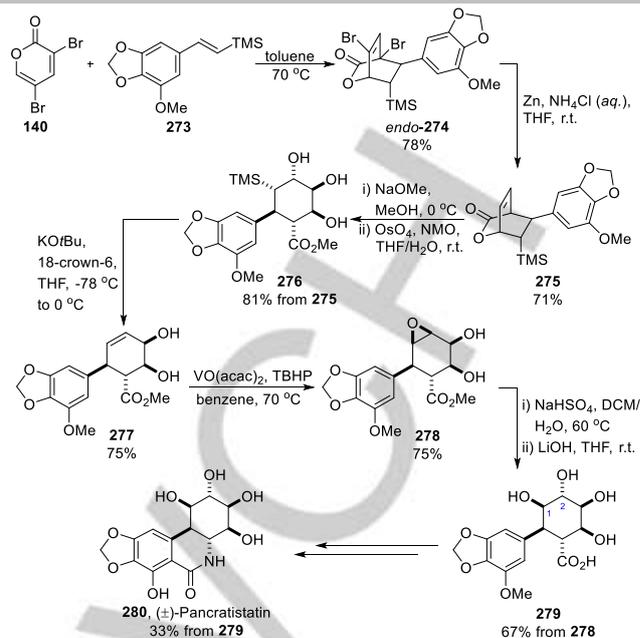
trans-Dihydronarciclasine is a natural isocarboxtyril alkaloid isolated from *Zephyranthes candida* in 1990, which exhibits excellent bioactivity against selected human cancer cell lines. The first total synthesis of (±)-*trans*-dihydronarciclasine was realized by Cho and co-workers in 2007, in which the initial step involved a highly *endo*-selective IEDDA reaction of 3,5-dibromo-2-pyrone **140** with styrene **142a**.^[45] As shown in Scheme 62, cycloadduct *endo*-**145a** was obtained in excellent isolated yield. Radical debromination of *endo*-**145** followed by acidic methanolysis afforded cyclohexene **265**. Direct exposure of **265** to OsO₄ in the presence of NMO provided triol **266** exclusively. Basic hydrolysis of the methyl ester furnished the corresponding carboxylic acid **267** which was then transformed into isocyanate **268** via Curtius rearrangement with diphenylphosphoryl azide. The isocyanate **268** was hydrolyzed into methyl carbamate **269**. Prior to construction of the pyridone ring, hydroxy groups were protected as acetic esters **270**. Subsequent Bischler–Napieralski reaction of **270** allowed to assemble pyridone ring and provided two regioisomers **271a** and **271b** in 3:1 ratio as an inseparable mixture. Finally, tetracyclic compound **271** underwent sequential demethylation and deacetylation to afford (±)-*trans*-dihydronarciclasine **272**.

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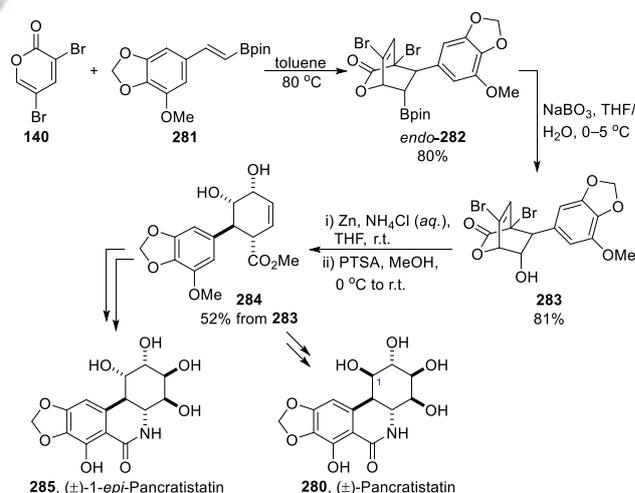
Scheme 62. Total synthesis of (±)-*trans*-dihydronarciclasine.

Structurally, pancratistatin, isolated from the bulbs of *Hawaiian Hymenocallis littoralis*, is highly similar to *trans*-dihydronarciclasine. Therefore, Cho and co-workers envisioned that the same synthetic strategy could be applied to the total synthesis of (±)-pancratistatin.^[46] As outlined in Scheme 63, (*E*)-β-silyl styrene **273** was used to participate in cycloaddition with 3,5-dibromo-2-pyrone **140**, leading to *endo*-selective adduct **274** in 78% yield. Subsequent treatment of lactone **274** with excess zinc powder in NH₄Cl solution resulted in debromination and afforded lactone **275** which sequentially underwent lactone opening and dihydroxylation to furnish triol **276**. Peterson elimination of β-hydroxysilane **276** provided cyclohexene **277** which was then treated with VO(acac)₂ in the presence of TBHP to afford epoxide **278**. Hydrolysis of the epoxide followed by ester hydrolysis provided carboxylic acid **279**. The same sequence as described above was applied to carboxylic acid **279**, allowing to assemble (±)-pancratistatin **280**.



Scheme 63. The total synthesis of (±)-pancratistatin.

In 2013, a modified synthetic strategy for the construction of (±)-pancratistatin and (±)-1-*epi*-pancratistatin was developed by the same group, starting from an IEDDA reaction between 3,5-dibromo-2-pyrone **140** and (*E*)-β-boryl styrene **281** (Scheme 64).^[47] Direct oxidation of cycloadduct *endo*-**282** with sodium perborate provided the corresponding alcohol **283**. Subsequent reductive debromination and acidic lactone opening afforded *cis*-1,2-diol **284** which could be transformed into (±)-1-*epi*-pancratistatin (**285**) by using the same sequence developed previously. Another sequence involving the stereochemical inversion of C1–OH function allowed to synthesize (±)-pancratistatin **280**.

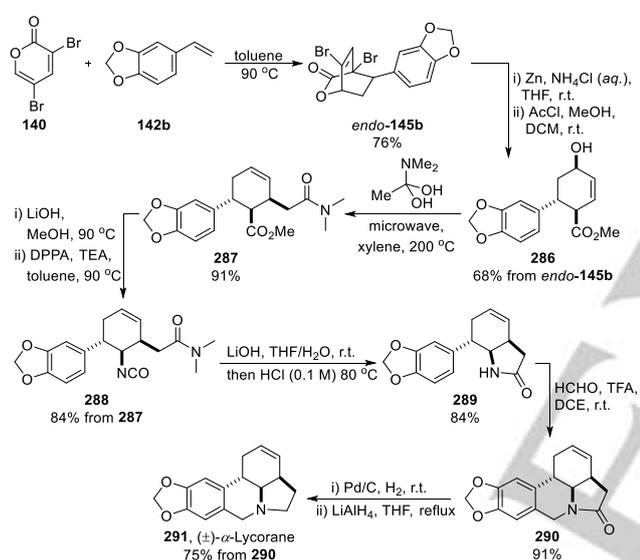
Scheme 64. The total synthesis of (±)-pancratistatin and (±)-1-*epi*-pancratistatin.

5.1.7. Total synthesis of lycorine-type alkaloids by Cho and co-workers

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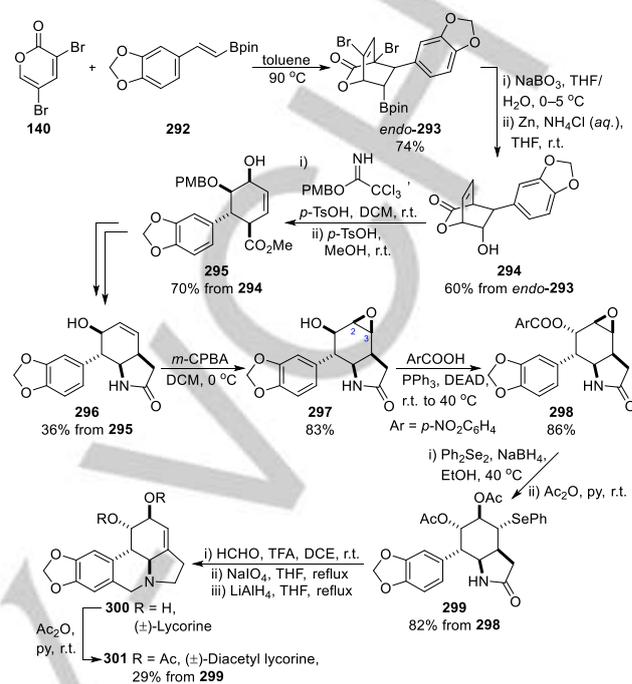
Lycorine-type alkaloids belong to the family of *Aspidosperma* alkaloids, the structure of which characteristically comprises a pyrrolo[de]phenanthridine common framework. In 2013, Cho and co-workers reported a novel synthetic route to two lycorine-type alkaloids (\pm)- α -lycorane and (\pm)-1-deoxylycorine by utilizing cycloadduct *endo*-145b as the key intermediate readily prepared from the IEDDA reaction of 3,5-dibromo-2-pyrone **140** with styrene **142b** (Scheme 65).^[48] The cycloadduct *endo*-145b was subjected to reductive debromination and acidic methanolysis to afford allyl alcohol **286**. Subsequent microwave-assisted Eschenmoser–Claisen rearrangement of allyl alcohol **286** with 1,1-dimethoxy-*N,N*-dimethylethanamine provided ester **287** which underwent sequential basic hydrolysis and Curtius rearrangement to furnish isocyanate **288**. Successive treatment of isocyanate **288** with LiOH and HCl allowed cyclization and delivered lactam **289** which was then subjected to Pictet–Spengler reaction and reductions to give (\pm)- α -lycorane **291**. Moreover, further elaboration of **287** allowed the synthesis of (\pm)-1-deoxylycorine.



Scheme 65. Total synthesis of (\pm)- α -lycorane.

In 2014, Cho and co-workers reported a modified strategy for the construction of (\pm)-lycorine (Scheme 66).^[49] (*E*)- β -Boryl styrene **292** participated in cycloaddition with 3,5-dibromo-2-pyrone **140** to provide lactone *endo*-293 which underwent oxidation by boronate and then reductive debromination to afford lactone **294**. The resulting hydroxyl group was protected as a PMB ether, followed by acidic methanolysis to deliver allyl alcohol **295**. The sequence developed previously was applied to **295**, delivering cyclohexene **296**. Subsequent epoxidation of C2–C3 double bond by *m*-CPBA furnished epoxide **297** with excellent diastereoselectivity due to the orientation of the pseudo-equatorial allylic hydroxyl group. However, direct ring-opening of the resultant epoxide **297** failed as the nucleophilic attack at C2 and C3 proceeded with little selectivity and provided an inseparable mixture. Interestingly, this problem could be overcome by the replacement of equatorial hydroxyl group by a large axially oriented substituent. Mitsunobu reaction of alcohol **297** with *p*-nitrobenzoic acid in the presence of PPh₃/DEAD followed by sequential ring-opening of the epoxide and protection of the resulting alcohol afforded lactam **299**. Finally,

299 was subjected to a sequence involving Pictet–Spengler reaction/selenoxide elimination /LiAlH₄ reduction to furnish (\pm)-lycorine (**300**) which was further converted into its diacetate derivative (**301**) for characterization.



Scheme 66. Total synthesis of (\pm)-lycorine.

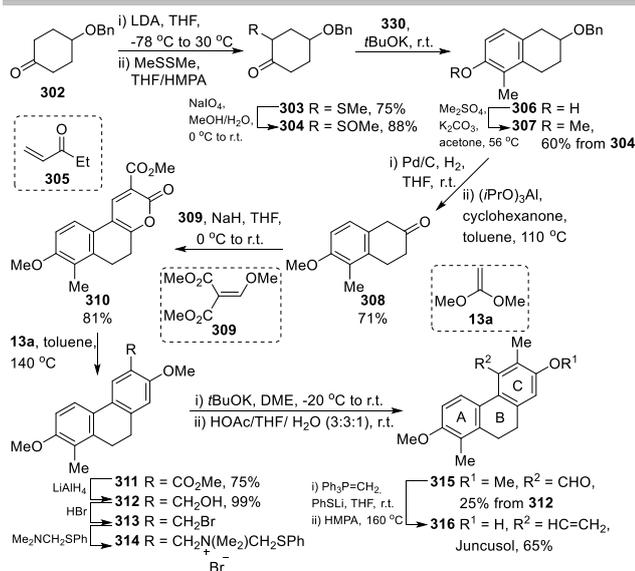
5.2. CO₂ extrusion

5.2.1. Synthesis of juncusol by Boger and co-worker

Juncusol (**316**) is a highly substituted 9,10-dihydrophenanthrene isolated from the extracts of needle rush *Juncus roemerianus*, and possesses antitumor and antimicrobial properties. In 1982, Boger and co-worker developed the total synthesis of juncusol in which aromatic ring A was introduced by Robinson annulation of β -keto-sulfoxide and aromatic ring C was constructed by an IEDDA reaction of 3-carbomethoxy-2-pyrone.^[77] As described in Scheme 67, oxidation of thioether **303** to β -keto-sulfoxide **304** was followed by Robinson annulation with ethyl vinyl ketone **305** to provide phenol **306**. Tetralone **308** was obtained by a three-step manipulation involving methylation of phenol, then removal of the benzyl protecting group and subsequent Oppenauer oxidation of the resulting alcohol, which was further converted into 3-carbomethoxy-2-pyrone **310** through Michael addition and intramolecular condensation. A sequence of IEDDA reaction/CO₂ extrusion/aromatization was carried out to forge aromatic ring C. Reduction of salicylate **311** with LiAlH₄ followed by bromination of the resulting primary alcohol afforded benzylic bromide **313**. Subsequently, the conversion of benzylic bromide **313** to quaternary ammonium salt **314** which was employed for a modified Sommelet–Hauser rearrangement, followed by aqueous acid hydrolysis furnished aldehyde **315**. The final conversion of aldehyde **315** to juncusol **316** was carried out by Wittig olefination and demethylation.

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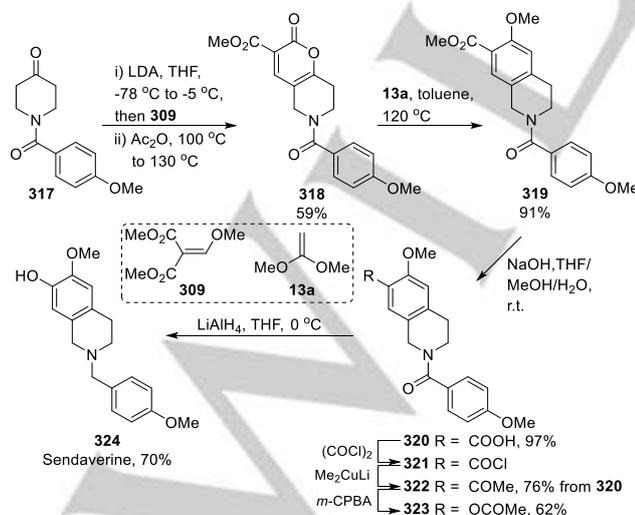
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Scheme 67. Total synthesis of juncosol.

5.2.2. Total synthesis of sendaverine by Boger and co-worker

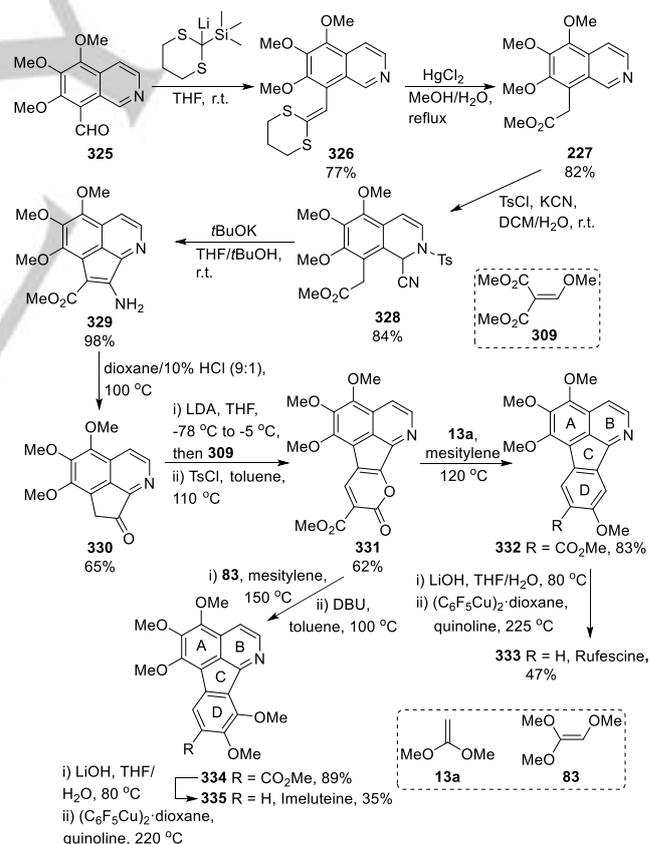
Sendaverine alkaloid (**324**) was isolated from *Corydalis aurea* and possesses a selectively protected *o*-catechol, which could be readily obtained by utilizing an IEDDA reaction of 3-carbomethoxy-2-pyrone. The total synthesis of sendaverine by this strategy was reported by Boger and co-worker in 1984.^[55] Conversion of ketone **317** to 3-carbomethoxy-2-pyrone **318** and subsequent treatment with 1,1-dimethoxyethylene **13a** at high temperature afforded salicylate **319** through the IEDDA reaction/CO₂ extrusion/aromatization sequence. Ester hydrolysis of **319** was followed by treatment with oxalyl chloride to form acid chloride **321** which was further transformed into ketone **322**. Baeyer–Villiger oxidation of ketone **322** furnished phenyl acetate **323**. Eventually, the synthesis of sendaverine **324** was accomplished by LiAlH₄ reduction of phenyl acetate **323** (Scheme 68).



Scheme 68. Total synthesis of sendaverine.

5.2.3. Total synthesis of rufescine and imeluteine by Boger and co-worker

Rufescine and imeluteine are azafluoranthene alkaloids isolated from bush ropes *Abuta imene* and *Abuta rufescens*. In 1984, Boger and co-worker developed a divergent approach to the preparation of rufescine (**333**) and imeluteine (**335**), the aromatic ring D of which was constructed by a sequence of IEDDA reaction/CO₂ extrusion/aromatization, as shown in Scheme 69.^[78] Condensation of aldehyde **325** with 2-lithio-2-(trimethylsilyl)-1,3-dithiane was followed by HgCl₂-promoted methanolysis of the resulting ketene thioacetal **326** to provide ester **327**. 1,2-Dihydroisoquinoline **328** was formed by treatment of **327** with *p*-TsCl in the presence of KCN in a two-phase reaction system. Exposure of **328** to *t*BuOK resulted in intramolecular annulation and furnished tricyclic compound **329**. Acid-promoted hydrolysis of **329** and subsequent decarboxylation afforded tricyclic ketone **330** in a single step. 3-Carbomethoxy-2-pyrone **331** was synthesized by a two-step operation from tricyclic ketone **330**. The sequence of IEDDA cycloaddition/CO₂ extrusion/aromatization was carried out to construct aromatic ring D and afforded tetracyclic compounds **332** and **334** by utilizing **13a** and **83** as dienophiles. Ester hydrolysis of **332** and **334** followed by decarboxylation provided naturally occurring rufescine (**333**) and imeluteine (**335**), respectively.



Scheme 69. Total synthesis of rufescine and imeluteine.

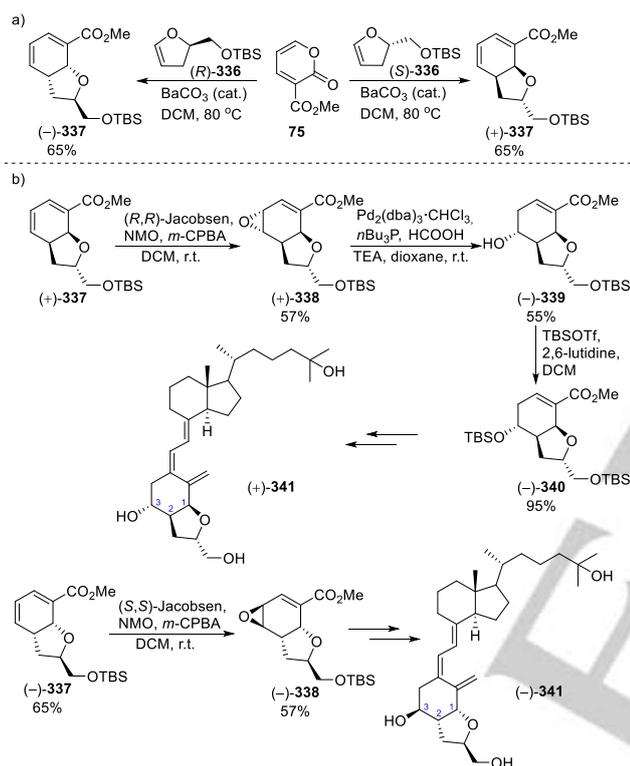
5.2.4. Total synthesis of tetrahydrofuran-fused calcitriol derivatives by Posner and co-worker

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In 2009, Posner and co-worker reported that 3-carbomethoxy-2-pyrone underwent diastereoselective IEDDA reactions with enantioenriched 2,3-dihydrofurans (*R*)-**336** and (*S*)-**336** as dienophiles followed by CO₂ extrusion, leading to cyclohexadienes (–)-**337** and (+)-**337**, respectively (Scheme 70a). Regio- and enantioselective epoxidation of the resulting cyclohexadiene (+)-**337** followed by a palladium-catalyzed ring-opening reaction and then O-silylation of the resulting alcohol afforded (–)-**340**. Bicyclic intermediate (–)-**340** was further elaborated into chiral tetrahydrofuran-fused calcitriol analog (+)-**341**. On the other hand, the diastereomer (–)-**341** was achieved when enantioenriched (–)-**337** was used as the starting material (Scheme 70b).^[79]

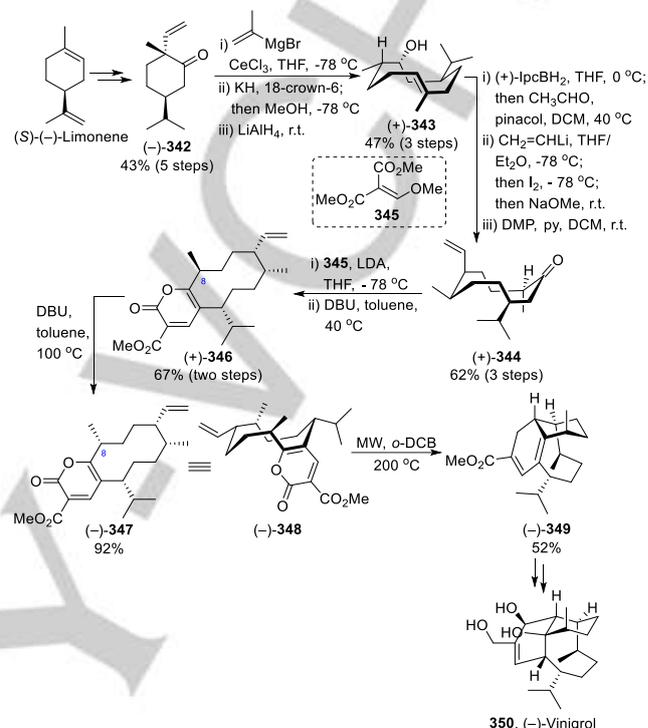


Scheme 70. Total synthesis of tetrahydrofuran-fused calcitriol derivatives.

5.2.5. Enantioselective total synthesis of (–)-vinigrol by Luo and co-workers

Vinigrol is a structurally complex terpenoid with a 6–6–8 tricyclic ring system, which possesses potent antihypertensive, platelet aggregation-inhibiting and antitumor properties. In 2019, Luo and co-workers completed the asymmetric synthesis of this diterpenoid (Scheme 71).^[80] Functionalized cyclohexanone (–)-**342**, obtained from commercially available (–)-limonene in 5 steps, was subjected to organocerium reagent, followed by oxy-Cope rearrangement and LiAlH₄ reduction to afford cyclodecene intermediate (+)-**343**. Cyclodecene (+)-**343** underwent diastereoselective pinene-controlled hydroboration, Zweifel olefination and Dess–Martin oxidation to provide cyclodecanone (+)-**344**, which could be converted to the desired 2-pyrone derivative (+)-**346**. Subsequently, (+)-**346** was epimerized to 2-pyrone (–)-**347** in boiling toluene in the presence of DBU. With 2-pyrone (–)-**347** in hand, the authors achieved a remarkable diastereoselective transannular IEDDA reaction under

microwave irradiation at 200°C. The resulting dienyl ester (–)-**349** was obtained with the cage skeleton of (–)-vinigrol after CO₂ extrusion. Further elaboration of (–)-**349** furnished (–)-vinigrol **350**. By this synthesis, Luo and co-workers demonstrate that the IEDDA reaction of pyrone is a robust reaction which can be applied to synthesize advance intermediates for further constructing complex molecules.



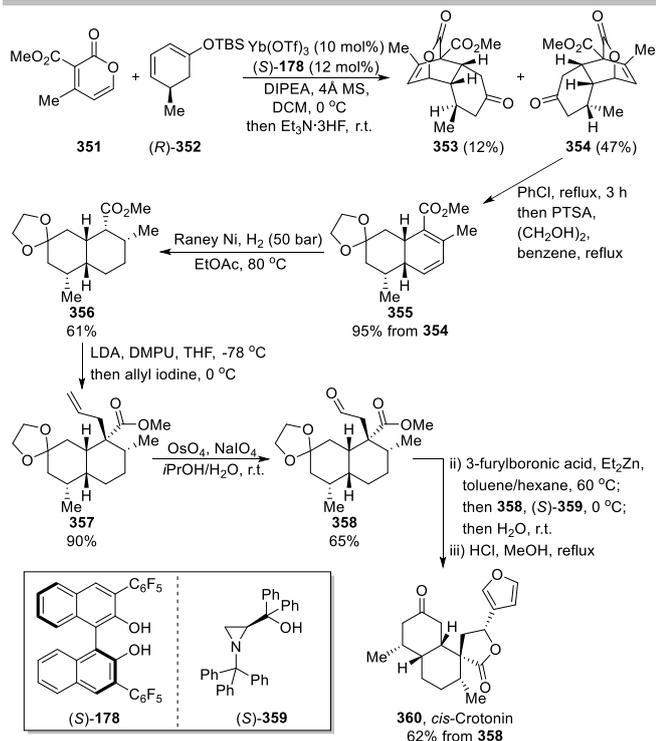
Scheme 71. Total synthesis of (–)-vinigrol.

5.2.6. Total synthesis of *cis*-crotonin by Cai and co-workers

Crotonins belong to clerodane diterpenes containing a decalin core structure. Recently, Cai and co-workers developed an efficient protocol for the synthesis of *cis*-decalins by using ytterbium-catalyzed asymmetric IEDDA reactions of 2-pyrone with silyl cyclohexadienol ethers and then completed the first total synthesis of *cis*-crotonin by late-stage transformation of the resulting *cis*-decalin.^[81] As shown in Scheme 72, starting from a stereodivergent IEDDA reaction of substituted 2-pyrone **351** and enantioenriched (*R*)-**352**, a pair of diastereomers was obtained in 12% and 47% yields after desilylation, respectively. Subsequent CO₂ extrusion from adduct **354** and protection of ketone with ethylene glycol provided dienyl ester **355** which was then subjected to Raney Ni in the presence of hydrogen to furnish *cis*-decalin **356**. Allylation of **356** delivered γ,δ -unsaturated ester **357** which possesses the same contiguous stereocenters as *cis*-crotonin. Further oxidation of terminal alkene by OsO₄/NaIO₄ afforded aldehyde **358**. Finally, diastereoselective 1,2-addition of aldehyde **358** with 3-furylzinc reagent, generated *in situ* from 3-furylboronic acid and diethylzinc, in the presence of chiral amino alcohol ligand (*S*)-**359**, followed by spontaneous lactonization and then hydrolysis of the ketal group completed the first total synthesis of *cis*-crotonin **360**.

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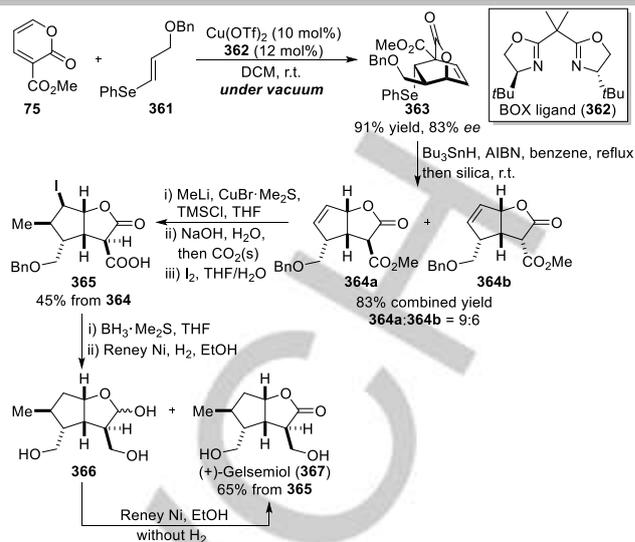


Scheme 72. Total synthesis of *cis*-crotonin.

5.3. Radical rearrangement

5.3.1. Enantioselective synthesis of (+)-gelsemiol by Gademann and co-workers

The enantioselective IEDDA reaction of 3-carbomethoxy-2-pyrone with vinylselenide was applied by Gademann and co-workers to complete the total synthesis of (+)-gelsemiol, an oxidized iridoid first isolated from *Gelsemium sempervirens*.^[82] As shown in Scheme 73, bicyclic lactone **363** was obtained in 91% yield and with 83% ee value by a Cu(OTf)₂/BOX ligand-catalyzed enantioselective IEDDA reaction under reduced pressure, followed by radical-mediated and acid-catalyzed skeletal rearrangements to deliver bicyclic fused lactones **364a** and **364b** as a diastereomeric mixture. Subsequently, lactones **364** underwent a four-step procedure involving methylation, lactone opening, ester hydrolysis and iodolactonization in one pot to furnish highly functionalized bicyclic fused lactone **365**. The reduction of carboxylic acid with excess BH₃·Me₂S followed by the removal of benzyl group and iodine atom with Raney nickel in the presence of ethanol and hydrogen provided lactol **366** together with natural product (+)-gelsemiol **367**. Interestingly, exposure of lactol **366** to Raney nickel in the absence of hydrogen also afforded (+)-gelsemiol.



Scheme 73. Total synthesis of (+)-gelsemiol.

6. Summary and Outlook

In the past few decades, great progress has been made in IEDDA reactions of electron-poor 2-pyrones as electrophilic dienes for construction of a great number of bridged lactones which are structurally related to many natural products and biologically relevant molecules. Under thermal conditions, the rigid lactone-bridged structure in the initially formed cycloadducts readily undergoes CO₂ extrusion *via retro*-DA cycloaddition to forge densely functionalized 1,3-cyclohexadienes and subsequent aromatization to afford polysubstituted aromatic compounds. Besides, the bridged lactones can also be attacked by a nucleophilic reagent to furnish densely functionalized cyclohexenes. The synthetic application of these attractive methodologies has been extensively studied for the preparation of numerous biologically active natural products and drug candidates.

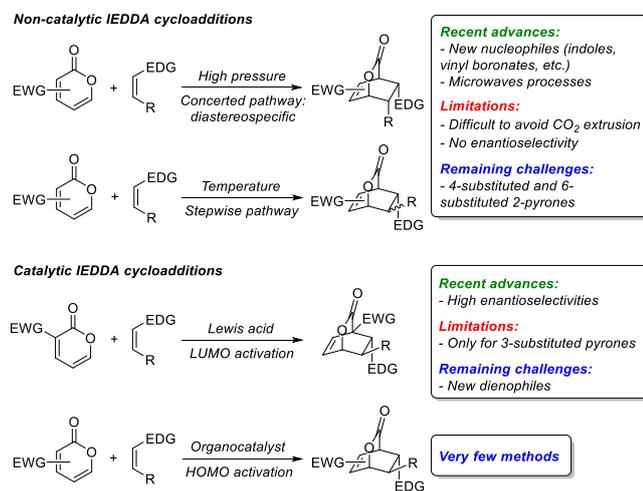
The use of Lewis acid catalysts can activate electrophilic 2-pyrones by lowering their LUMO level, for which corresponding IEDDA reactions with electron-rich dienophiles could occur under relatively mild conditions and provide bridged lactones exclusively. On the other hand, the use of aminocatalyst allows to expand the substrate scope to α,β -unsaturated carbonyl compounds because of the formation of electron-rich dieneamine intermediates *via* condensation. Remarkably, both Lewis acid catalysis and aminocatalysis can realize direct asymmetric induction, avoiding tedious operations in the conventional auxiliary-based approach.

However, in most cases dienophiles for IEDDA reactions are limited to highly activated, monosubstituted, electron-rich alkenes, such as vinyl ethers, which significantly limits the application of these efficient methods; thus the investigation of different dienophiles is still in great demand. Moreover, catalytic IEDDA reactions based on LUMO-activation strategy usually rely on 3-substituted 2-pyrones, the 1,3-dicarbonyl structure of which could serve as a good handle for the catalyst, but other substitution patterns of the 2-pyrone are not suitable for this type of activation. The HOMO-activation approach through organocatalysis, although still in its infancy, provides an attractive alternative to expand the scope of catalytic enantioselective IEDDA reactions of 2-pyrones bearing different

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substitution patterns. We anticipate that this approach will inspire the development of many new synthetic methodologies in the future, along with their application to enantioselective natural product synthesis. Therefore, the development of novel, general catalytic systems for IEDDA reactions of electrophilic 2-pyrones with excellent chemo-, regio- and stereocontrol, and further application of these practical, efficient protocols remains a promising area that is worth deeply researching.



Scheme 74. Summary of recent advances and remaining challenges.

Abbreviations

Ac	acyl
Ad	adamantyl
AIBN	2,2'-azoisobutyronitrile
AM1	Austin Model 1
Ar	aryl
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
Cbz	carboxybenzyl
Cy	cyclohexyl
DABCO	diazabicyclooctane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
DIBAL-H	diisobutylaluminum hydride
DIPEA	<i>N,N</i> -diisopropylethylamine
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide
DMP	Dess–Martin periodinane
DMPU	1,3-dimethyl-propyleneurea
DMSO	dimethyl sulfoxide
DPPA	diphenylphosphonic azide
EDG	electron-donating group
EWG	electron-withdrawing group
HMPA	hexamethylphosphoramide
HOMO	highest occupied molecular orbital
Ipc	isopinocampheyl
LA	Lewis acid
LDA	lithium diisopropylamide
LUMO	lowest unoccupied molecular orbital

<i>m</i> -CPBA	<i>m</i> -chloroperoxybenzoic acid
MOM	methoxymethyl
Ms	mesyl
MS	molecular sieves
MW	microwave
Nap	naphthyl
NMO	<i>N</i> -methylmorpholine oxide
<i>o</i> -DCB	<i>o</i> -dichlorobenzene
PCC	pyridinium chlorochromate
Phth	phthaloyl
PM3	Parametric Method 3
PMB	<i>p</i> -methoxybenzyl
PTSA	<i>p</i> -toluenesulfonic acid
py	pyridine
TBAF	tetrabutylammonium fluoride
TBDPS	<i>tert</i> -butyldiphenylsilyl
TBHP	<i>tert</i> -butyl hydroperoxide
TBS or TBDPS	<i>tert</i> -butyldimethylsilyl
TEA	triethylamine
Tf	triflyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMS	trimethylsilyl
Tol	tolyl
Ts	tosyl
TTMSS	tris(trimethylsilyl)silane

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Keywords: Diels–Alder reaction • Inverse-electron-demand • 2-Pyrene • Synthetic methods • Total synthesis

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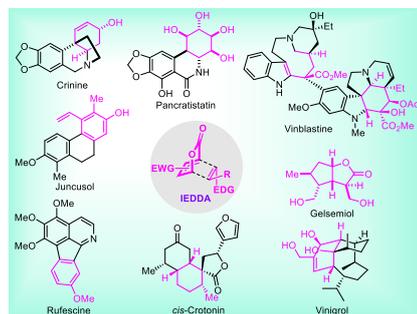
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Inverse-electron-demand Diels-Alder (IEDDA) reactions of electrophilic 2-pyrones as dienes have been extensively studied in the past. In this review, the developments of these IEDDA reactions including non-catalytic, Lewis acid-catalyzed and organocatalytic IEDDA reactions, and their applications in the total synthesis of natural products and drug candidates are discussed.

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