Organic & Biomolecular Chemistry

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/obc

Organic & Biomolecular Chemistry

REVIEW

4π Electrocyclisation in domino processes: contemporary trends and synthetic applications towards natural products

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Nadeem S. Sheikh[a]

Recent most instructive and reliable literature reports which deal with domino processes involving conrotatory 4π electrocyclic reactions, along with a precise mechanistic insight and latest synthetic applications towards biologically active natural products are concisely reviewed. To inspire further research in this domain, a tangible intuition about overarching emerging themes and potential imminent prospects are also delineated.

1 4π Electrocyclisation: a comprehensive account

From structurally complex bioactive architecture to synthetically significant intermediates, carbocyclic compounds are common motifs present in modern synthetic chemistry. Among various established methodologies towards the synthesis of such molecules, electrocyclisation is one of the most attractive, and an instrumental approach that proceeds with an excellent and predictable regio- and stereocontrol.[1] Electrocyclisation is prevalent in organic chemistry and are based on Woodward-Hoffmann's rules that explain the stereochemical outcome of an electrocyclic transformation by recognising the symmetry of frontier orbitals.[2] These are the key orbitals which manifest the bond breaking and making processes of a concerted reaction.

In the list of several available modes of electrocyclisation, 4π electrocyclisation (π_a^4) is conspicuous. It has been articulately incorporated to accomplish the synthesis of a large number of intriguing polycyclic molecules such as (±)-tetrapetalone A-Me aglycon (**1**),[3] taiwaniaquinone H (**2**),[4] (±)-methyl rocaglate (**3**),[5] (±)-rocaglamide (**4**),[6] cribrostatin 6 (**5**),[7] (±)-cephalotaxine (**6**),[8] (±)-roseophilin (**7**),[9] nakiterpiosin (**8**),[10] (±)-merrilactone A (**9**),[11] and (–)-scabronine G (**10**,[12] Fig. 1). These compounds are associated with potent cytotoxicity against cancer cells, multidrug resistance tumours and possess substantial bioactivities including antimicrobial, anti-leukamic, anti-inflammatory, antineoplastic and insecticidal activities. Thus these polycyclic compounds have attracted a lot of interest from the synthetic community.

Depending on the number of atoms involved in the electrocyclisation step, 4π electrocyclisation is broadly classified into two distinctive systems *i.e.*, 4π-electron-4-atom and 4π-electron-5-atom. A generic representation of some significant conrotatory 4π electrocyclic reactions is demonstrated in Fig. 2, which have been successfully incorporated in a cascade process. A classical methodology which provides an expedient access into substituted cyclobutenes involves 4π-electron-4-atom system. Cyclobutene motif[13] is a core structural unit in a number of natural products and can be generated from butadienes[14] (Fig. 2, a), vinyl allenes[15] (Fig. 2, b) and allene-enamines[16] (Fig. 2, c). Formation of β-lactam by the nucleophilic attack of an imine on a ketene is also proposed to undergo 4π electrocyclisation *via* the formation of zwitterionic intermediate, and this reaction is termed as Staudinger reaction.[17a] It has been proposed that this type of transformation is not truly pericyclic and should be considered as an intramolecular Mannich-type reaction.[17b] However, another argument advocates that the cyclisation of zwitterionic intermediate may be regarded as an interaction between the HOMO of enolate π and the LUMO of iminium π*, which results into a conrotatory cyclisation.[17c]

A phenomenal and extensively studied approach to construct richly functionalised cyclopentenones in a regio- and stereoselective manner is Nazarov cyclisation, which falls in the category of 4π-electron-5-atom strategy.[18] These can be accessed *via* 4π conrotatory electrocyclic ring-closure reactions of substituted cross-conjugated divinyl ketones[19] (Fig. 2, d), allenyl vinyl ketones[20] (Fig. 2, e) and furylcarbinols[21] (Fig. 2, f). In case of furylcarbinols (Fig. 2, f), 4π conrotatory electrocyclisation is a key step of this conversion known as Piancatelli rearrangement and an aza-version[22] of this rearrangement has also been documented. Despite of the fact that 4π electrocyclisation-mediated mechanism is widely accepted and reported for Piancatelli rearrangement, aldol-type[23a] and zwitterion-induced[23b] mechanisms have also been proposed.

[a] *Department of Chemistry, Faculty of Science, King Faisal University P.O. Box 380, Al-Ahsa 31982, Saudi Arabia Tel: (+966) 13-589-9574, (+966) 58-224-6803; Fax: (+966) 13-588-6437 E-mail: nsheikh@kfu.edu.sa, n.sadiq.s@gmail.com*

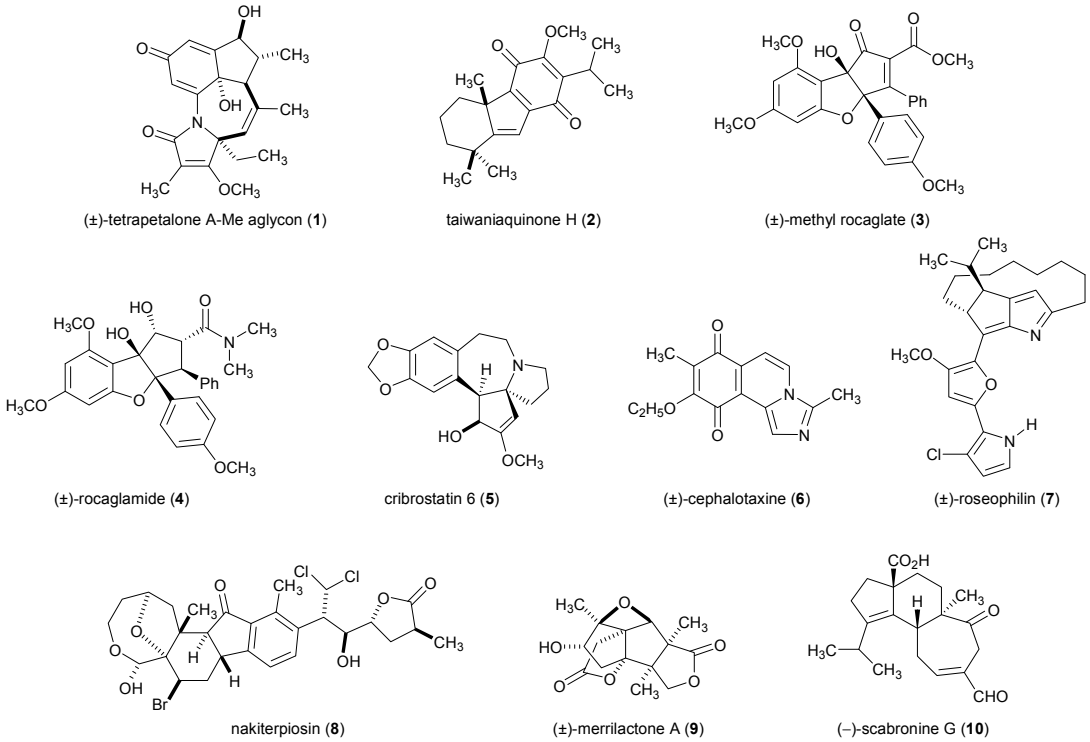


Fig. 1 Structures of representative natural products with bioactive characteristics, obtained by employing 4π electrocyclisation strategy.

Alongside classical Nazarov cyclisation which relies on a divinyl ketone substrate (Fig. 2, d), aza-, imino-, oxo-, and homo-Nazarov cyclisations have also been developed.[24] Moreover, triazoles have been utilised to prepare substituted pyrroles (Fig. 2, g).[25] These five-membered carbocyclic structures are vital building blocks in organic chemistry and constitute core segments of many biologically active natural products.

Quantum chemical calculations have revolutionised the art of synthesis and are inevitably associated to gain an insightful information towards the elucidation of reaction pathways and chemical reactivity descriptors.[26] Over last few years, application of computational investigations in synthesis has emerged as an indispensable research element. This kind of theoretical study is, indeed, a time and cost effective as well as an efficient and reliable source to predict the mechanism and molecular properties. Most of the research articles dealing with pericyclic reactions including domino 4π electrocyclic ring-closure strategies describe the use of computational studies to support the experimental results and these are highlighted in the respective sections of this account. Additionally, torquoselectivity that explains the selectivity of inward or outward rotation of the substituents in the 2-position of a cyclobutene is appropriately described in the related context for 4π electrocyclic ring-opening reactions in a domino process.[27]

The prime focus of this review is to summarise the recent most instructive examples of domino reactions that include 4π electrocyclisation. Also, a precise mechanistic insight and latest synthetic applications are delineated, which draw an attention towards the scope and synthetic utility of such protocols in the domain of bioactive natural products. To inspire further research on domino reactions involving 4π electrocyclisation, a real insight about overarching emerging themes and potential leading future directions are also provided.

2 Domino reactions in 4π electrocyclisation

Domino or tandem processes in synthesis have gained enormous consideration due to assorted advantages, which include reaction efficacy by alleviating time, handling efforts, reduction of waste, improved atom economy and above all, construction of a complex architecture from simple organic molecules effectively in a single operation.[28] Due to this, the art of organic synthesis has inclined towards sustainable cascade pathways. A quick shuffling of the latest literature reveals that the number of research articles describing a one-pot–multi-steps synthesis has profoundly increased. However, not every reaction of such type falls in the category of a true domino process, which involves two or more bond–forming reactions that occur in a cascade in one-pot. Moreover, latter transformations take place at the functionalities, which are generated in the former steps. As sequential reactions in the same pot are involved, this chemistry has a potential to build complex molecular structures, which are difficult to obtain by other means. Therefore, this strategy has been successfully applied for a regio- and stereoselective synthesis of polycyclic and other challenging molecular structures of interest.

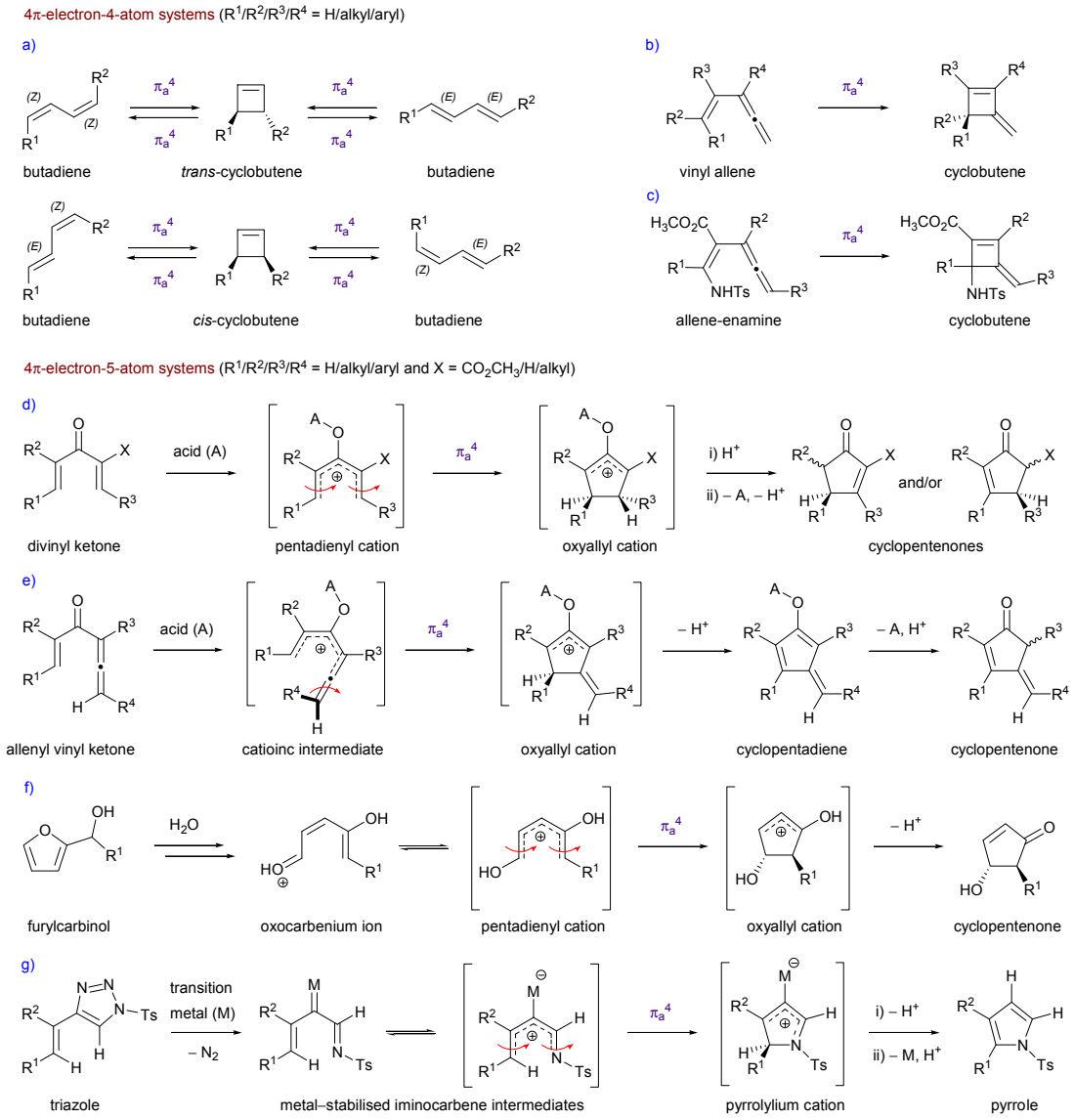


Fig. 2 Generic examples of conrotatory 4π electrocyclic reactions towards the synthesis of carbocyclic compounds prepared from (a) butadiene, (b) vinyl allene, (c) allene-enamine, (d) divinyl ketone, (e) allenyl vinyl ketone, (f) furylcarbinol, and (g) triazole.

In this section, recent most reliable and synthetically significant examples are precisely described, in which, 4π electrocyclisation is exquisitely combined in a domino process. The other reaction is either a rearrangement, cyclisation or a renowned synthetic transformation. To highlight the significance of 4π electrocyclisation in domino reactions and to facilitate the scientific community, each unit is classified into sub-units, based on the products obtained from these processes. In addition to this, recent applications of domino reactions involving conrotatory 4π electrocyclic ring-closure transformation in natural product total syntheses have been reported with respect to the challenges and accomplishments, while keeping noteworthy aspects of the routes as equally important considerations.

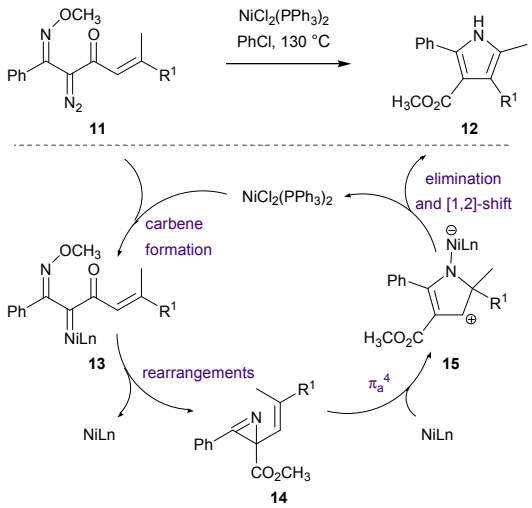
2.1 Rearrangement–4π electrocyclisation protocol

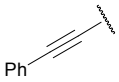
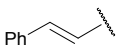
Rearrangement is a crucial conversion which arises by an intramolecular repositioning of atoms through the involvement of the sigma bond. There are numerous elegant reports that deal with rearrangements combined with 4π electrocyclisation in a single step and this section provides a concise overview of the most recent and representative ones.

2.1.1 Pyrroles

Pyrroles are an architectural underpinning of numerous natural and synthetic compounds of significant biological activities. Park and Jiang have recently developed a nickel-promoted catalytic process which manifests the formation of pyrrole **12** from an α-diazo oxime

ether **11** (Scheme 1).[29] The reaction works equally well with a range of substituents such as alkyl, aryl and heteroaryl groups. Additionally, cyclic oxime ethers are also subjected to access bicyclic pyrroles in good yields. Mechanistically, the reaction proceeds *via* the formation of carbenoid **13**, which undergoes sequential rearrangements to give vinyl azirine **14**. At this juncture, 4π electrocyclisation takes place to generate an intermediate **15** followed by reductive elimination of the metal and [1,2]-substituent shift leading to the desired pyrrole product **12**. Interestingly, a judicious choice of the catalyst such as $Rh_2(OAc)_4$ instead of $NiCl_2(PPh_3)_2$ alters the reactivity and results into pyridine through prototropic isomerisation followed by 6π electrocyclisation.

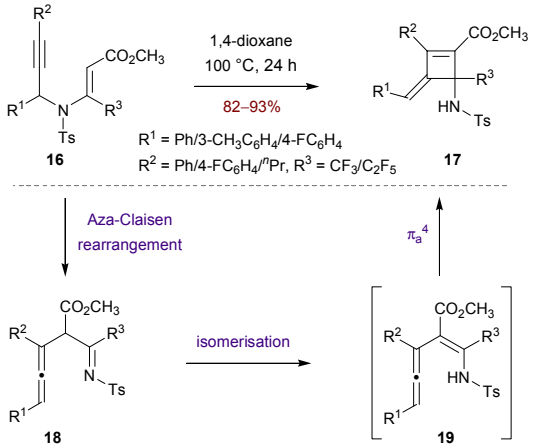


R^1	yield (%)	R^1	yield (%)
CH_3	82	$(CH_3)_3C$	67
Ph	80		72
	92		84

Scheme 1 Synthesis of substituted pyrrole **12** from α-diazo oxime ether **11** by employing rearrangement–4π electrocyclisation cascade.[29]

2.1.2 Polyfluoroalkyl cyclobutenes

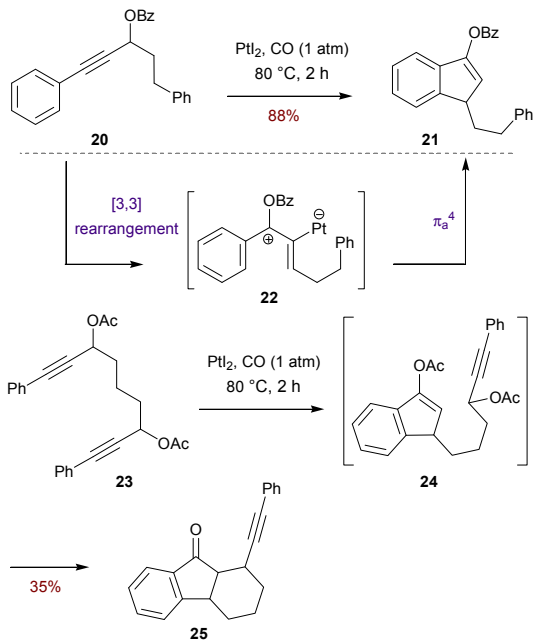
Wan and co-workers reported an effective thermal aza-Claisen rearrangement–4π electrocyclisation domino process to access highly substituted polyfuoroalkyl functionalised cyclobutene **17** from 3-aza-1,5-enyne **16** (Scheme 2).[16] After initial rearrangement, isomerisation of the resultant allene-imine intermediate **18** provides an allene-enamine **19**, which subsequently undergoes 4π electrocyclisation to generate cyclobutene **17** with an exocyclic olefinic bond. The proposed mechanism is supported by deuterium-labelling experiment and kinetic studies performed by ^{1}HNMR spectroscopy. A variety of functionalised cyclobutenes are readily achievable by this route in an excellent yield and the reaction tolerates a range of aryl groups bearing electron-neutral, -withdrawing, -donating and halogen species.



Scheme 2 Thermal aza-Claisen rearrangement–4π electrocyclisation approach to prepare polyfluoroalkyl cyclobutene **17**.[16]

2.1.3 Indanones

Indanones constitute a core skeleton for several natural products and a platinum-promoted catalytic platform to prepare 3-substituted indanone derivatives such as **21** from propargylic ester **20** has been designed by She and colleagues (Scheme 3).[30]



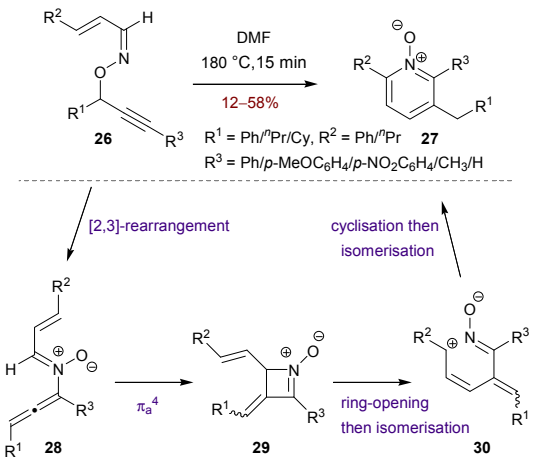
Scheme 3 [3,3]-Rearrangement and 4π electrocyclisation in a cascade to construct carbocyclic compounds **21** and **25**.[30]

The reaction pathway comprises of [3,3]-rearrangement to furnish a 4π-electron-5-atom containing cation **22**, which on conrotatory 4π

electrocyclic ring-closure gives indanone **21** through the loss of an adjacent proton in the resultant cyclopentenyl cation. The chemistry is well tolerant to electron-donating groups on the aryl substituents and has been extended to achieve the synthesis of 3,3-disubstituted indanones by employing tertiary arylpropargylic acetates. Furthermore, bis-propargylic ester **23** was converted to a tricyclic carbocycle **25** *via* an intermediate **24**, which results from [3,3]-rearrangement–4π electrocyclisation tandem sequence and subsequent 6-*exo*-*tet* cyclisation.

2.1.4 Pyridine oxides

A highly regioselective approach to prepare polysubstituted pyridine oxide **27** from *Z*-propargylic oxime **26** involves [2,3]-rearrangement leading to a rotamer of *N*-allenylnitrone motif **28**, ready for electrocyclisation to generate cyclic nitrone **29** (Scheme 4).[31] Formation of zwitterionic intermediate **30** from the nitrone **29** is plausible as a result of ring-opening and isomerisation, which cyclises to the desired pyridine oxide **27**. Overall, the reaction yield for this domino process is moderate however the regioselectivity is excellent and it suggests a neat and sustainable approach to construct pyridine oxide from readily available propargylic oximes.



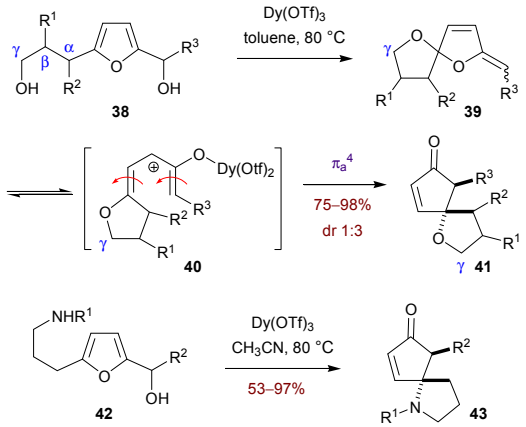
Scheme 4 A sustainable approach towards polysubstituted pyridine oxide **27**.[31]

2.1.5 4-Hydroxycyclopentenones

A well-established protocol to access 4-hydroxycyclopentenone scaffold **35** is an acid-promoted rearrangement cascade applied to furylcarbinol **31** (Scheme 5) and it has been extensively studied in the laboratory of de Alaniz.[32] A series of cascading transformations *via* oxocarbenium intermediates **32** and **33** occur to install a pentadienyl cation **34**, which furnishes the desired 4-hydroxycyclopentenone **35** after 4π electrocyclisation. The substrate scope is not limited to alkyl substituents; aryl substituted furylcarbinol **36** leads to the corresponding cyclopentenone **37** as well. In general, alkyl substituents are more challenging as well as sluggish and to overcome this, a dual Lewis/Brønsted acid catalyst system has been applied successfully. Sub-stoichiometric amounts of the catalysts, alkyl and aryl substituted furylcarbinols and exclusive formation of a single *trans*-diastereomeric product are the key attributes of this synthetic transformation.

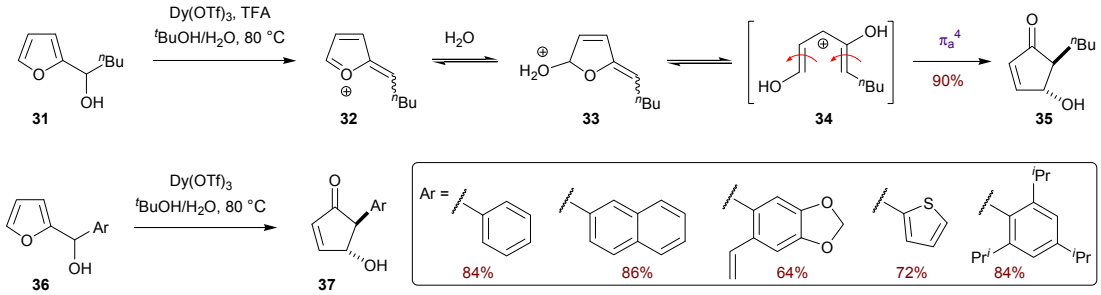
2.1.6 Spirocyclic ethers and Azaspirocycles

Spirocyclic compounds are present in numerous biologically active molecules and their synthesis is often thwarted by the difficulties encountered during the formation of heteroatom substituted quaternary stereocentres. An application of furan derivative **38** under acidic conditions demonstrates the formation of spiroketal enol ether **39**, which subsequently transforms into cationic intermediate **40** (Scheme 6).[33] Then, a 4π electrocyclic reaction of the intermediate **40** affords the spirocyclic ether **41**.



Scheme 6 de Alaniz's strategy for spirocyclic ether **41** and amine **43**, based on Lewis acid catalysis.[33,34]

The effect of substituents at α, β, and γ positions relative to the furan ring has been investigated, which does not substantially influence the torquoselectivity of the 4π electrocyclisation step and

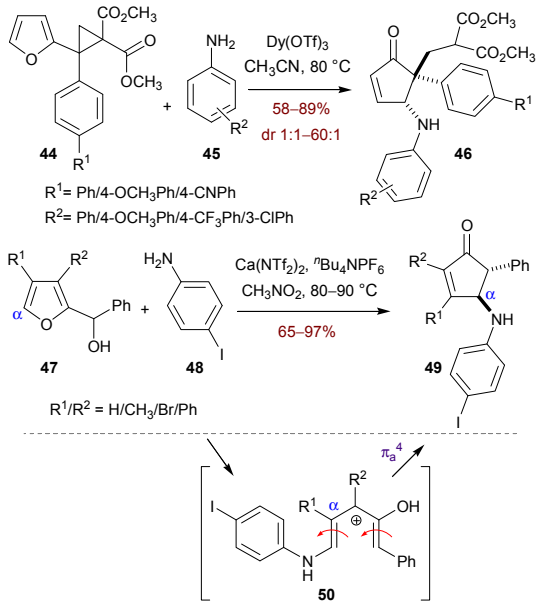


Scheme 5 Acid-catalysed Piancatelli rearrangement involving 4π electrocyclisation to prepare 4-hydroxycyclopentenones **35** and **37**.[32]

a moderate diastereoselectivity is observed. Also, azaspirocycle **43** has been prepared in the same manner as an exclusive *trans*-diastereomer from the furan motif **42** and the *trans*-selectivity was confirmed by single-crystal X-ray analysis of the product (Scheme 6).[34] The reaction is high yielding, tolerant to an array of substituents on aryl groups and has also been applied to access 6-azaspirocyclic compounds.

2.1.7 4-Aminocyclopentenones

An aza-version of Piancatelli rearrangement was achieved by the reaction of substituted aniline **45** with cyclopropane scaffold **44** to obtain aminocyclopentenone **46**, bearing a congested vicinal stereocentre in good to excellent yields and high diastereoselectivity (Scheme 7).[35] Notably, electron-rich aryl substituents substantially enhance the diastereoinduction as compared to simple aniline substrate and an electron-deficient group as R^1 hinders the cascade rearrangement. It is probably because the products from these cyclopropane derivatives are less stable and undergoes a rapid intramolecular Micheal addition, leading to bicyclic compounds. The reaction proceeds smoothly at ambient conditions however, an interesting finding reveals an inverse relation of temperature with the stereocontrol of this transformation; the optimum temperature was found to be 80 °C. To investigate the rate of reaction and gain a detailed mechanistic insight about the factors affecting the catalytic pathway for this synthetic transformation, Hein and colleagues performed an extensive kinetic studies.[36] It was found that the nucleophilicity of aniline derivative **45** and it's off-cycle binding with the acid catalyst plays a decisive role in the initial formation of an oxocarbenium ion that triggers the rearrangement cascade, terminating into a conrotatory 4π electrocyclic ring-closure reaction.



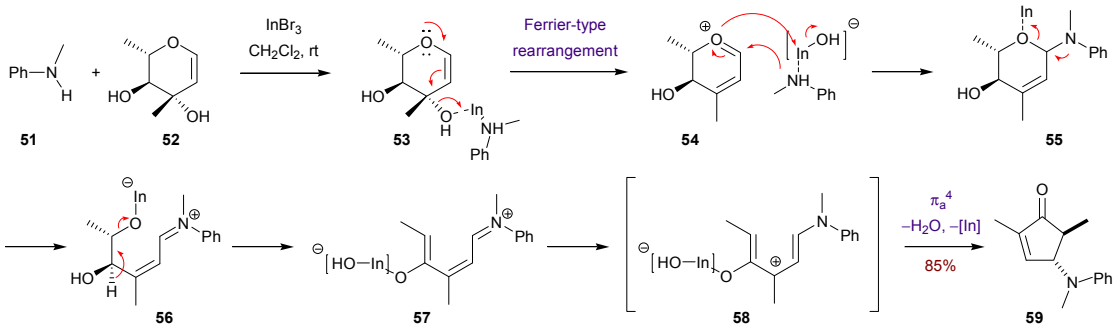
Scheme 7 Synthesis of 4-aminocyclopentenones **46** and **49** *via* Aza-Piancatelli rearrangement.[35,37]

Application of environmentally benign alkali and alkaline-earth metal complexes in synthetic chemistry, particularly of calcium complexes is an attractive approach due to a continuous need for sustainable reagents and chemical processes. Moreover, ubiquity of alkaline-earth metals in the environment is a distinct advantage over rare metals for industrial processes and their minimal toxicity is beneficial in both handling and disposal. The first examples of calcium-mediated variant of aza-Piancatelli rearrangement discloses the reaction of substituted furylcarbinol **47** with *p*-iodoaniline (**48**) to offer 4-aminocyclopentenone **49** in a good yield (Scheme 7).[37] Combination of ammonium salt with the calcium reagent markedly enhances the reaction efficiency in terms of time and yield, though it is not strictly required for this transformation. After series of initial rearrangement and nucleophilic addition of aniline **48** to the resultant oxocarbenium species, a pentadienyl carbocation **50** is formed, which undergoes 4π electrocyclisation to give the desired product **49**. It is a practical methodology and a range of substituted furylcarbinols and anilines are amenable to the reaction conditions. Not surprisingly, the nucleophilic attack of aniline **48** on the intermediate oxocarbenium ion is restricted by the steric bulk at α-carbon of the furylcarbinol **47**. Substitution of hydrogen atom with methyl group at the α-carbon leads to decomposition of the substrates.

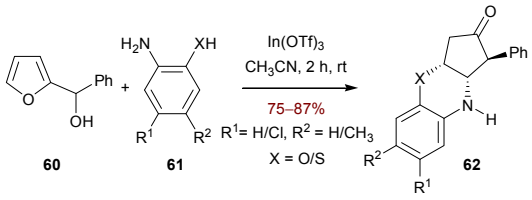
Yao and Zhang along with their co-workers have demonstrated the formation of indium-promoted 4-aminocyclopentenone **59** by the reaction of *N*-methylaniline (**51**) with glycal **52** (Scheme 8) and its application towards biologically active 4-aminocarbocyclic nucleosides.[38] A metal coordinated pyran structure **53** leads to an oxocarbenium ion **54** through Ferrier-type rearrangement, which is ring-opened to ammonium species **56** *via* tertiary amine **55**. Pull-push electronic follow induced by the nitrogen atom leads to an isomeric structure **57**, which subsequently generates a stable pentadienyl cation **58** that follows 4π electrocyclic pathway to end up into the required *trans*-selective cyclopentenone **59** exclusively. This catalytic system has proven tolerance towards aryl- or heteroarylamines and variously substituted glycals. Treatment of an excess of glycal substrate (2 eq.) with substituted phenylanilines affords corresponding over-reacted product in a noticeable amount (up to 32%) along with the desired 4-aminocyclopentenones.

2.1.8 Benzo[*b*][1,4]oxazines and thiazines

Cyclopentenones lend well to 1,4-Micheal addition and this possibility has been explored in a cascade by Reddy and co-workers.[39] Treatment of furylcarbinol **60** with polysubstituted analine **61** represents a generic approach of the tandem sequence to construct benzo[*b*][1,4]oxazine and thiazine scaffold **62** (Scheme 9). After successful aza-Piancatelli rearrangement a *trans*-selective cyclopentenone intermediate is formed, which immediately undergoes an intramolecular 1,4-Micheal addition with a complete stereocontrol to afford the desired products in good yields. The process is viable to generate a library of oxazines and thiazines however the reported scope for both starting materials dwarfs the synthetic visibility of this transformation.



Scheme 8 Glycosidation of *N*-methylaniline (**51**) to access substituted 4-aminocyclopentenone **59**.[38]



Scheme 9 Aza-Piancatelli rearrangement–Micheal reaction in domino process to prepare benzo[*b*][1,4]oxazines and thiazines **62**.[39]

2.1.9 Indenes

Yu and co-workers have investigated a comprehensive DFT calculations based mechanistic study for the synthesis of substituted indenes through platinum$^{(II)}$ chloride-initiated sp^3 C–H activation of *ortho*-isopropyl substituted aryl alkynes.[40] The reaction has also been reported with variously substituted terminal alkynes like bromo-substituted compound **63**, which affords an exclusive formation of indene substrate **64** in an efficient manner (Scheme 10). Swapping bromine with a phenyl group substantially affects the yield (52%) despite of an increased reaction time and it also leads to incorporation of phenyl group at C-2 position of the resultant indene as observed in the reaction of alkyne **65** to furnish the indene structure **66**. To rationalise the obtained products with complete regio-specificity, this transformation is believed to follow different routes. After initial coordination of platinum$^{(II)}$ chloride with the alkyne motif of aryl alkyne **67**, an endo vinyl cation **68** is formed with three possible pathways to proceed further (Scheme 10). According to DFT calculations, the fate of the zwitterionic species **68** is regulated by the terminal substituent (R^1) on the alkyne functionality; a hydrogen or bromide group follows the route A, while an alkyl group ends up into the corresponding product through the route C. This is primarily because of difficulties in [1,2]-alkyl migration. In case of an aryl substituent on the terminal alkyne, the route B might also be a possible pathway.

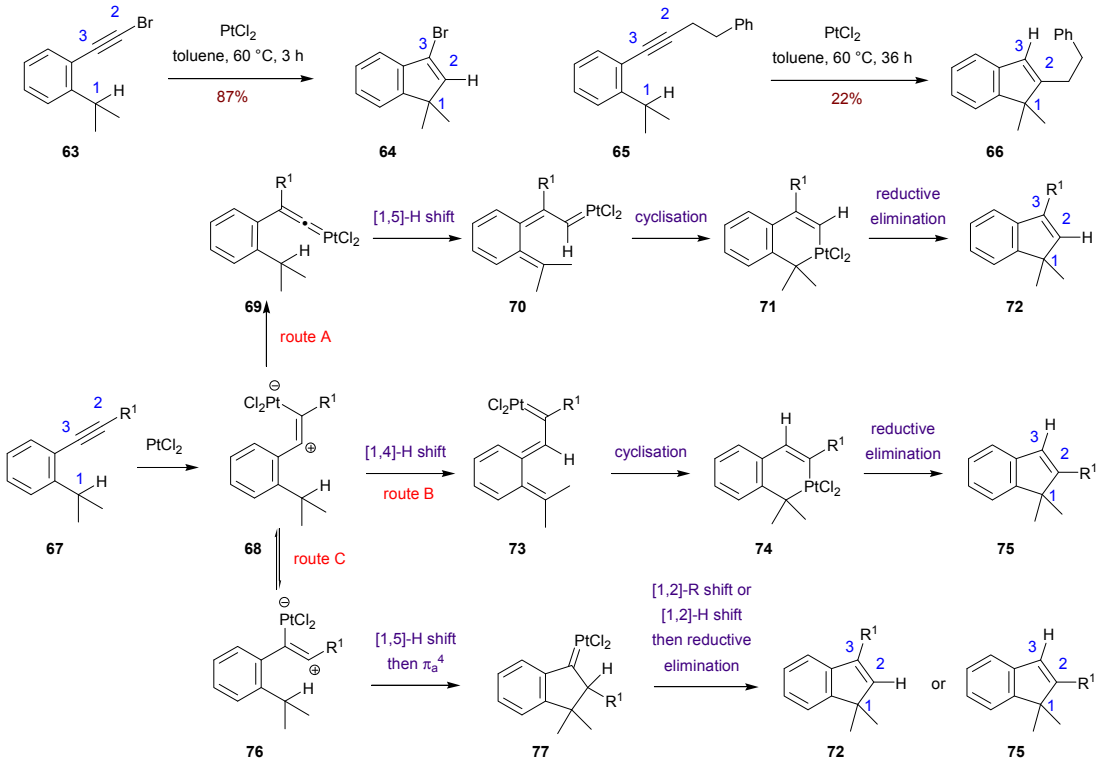
Endo vinyl cation **68** undergoes [1,2]-R^1 migration to form platinum vinylidene **69** *via* a platinum–π alkyne complex, which subsequently passes through [1,5]-H shift to generate metallohexatriene **70** (route A). At this stage, a six-electron electrocyclisation results into a metallacycle **71**, which on reductive elimination gives the indene product **72** with R^1 substituent relocated to C-3 position. Another mechanistic approach, route B, involves the formation of platinum–carbene complex **73** from cationic intermediate **68** *via* [1,4]-H shift followed by electrocyclised product **74**, which leads to the elimination of platinum to provide the indene substrate **75** with R^1 substituent at the original C-2 position. A different possibility supported by DFT computations is the formation of exo vinyl cation **76** from cation **68**, ready for [1,5]-H shift followed by 4π electrocyclic ring-closure to give an intermediate **77**, which can produce indene products **72** or **75** through [1,2]-R^1 or [1,2]-H shift respectively.

2.2 4π Electrocyclisation–rearrangement strategy

4π Electrocyclisation involving 5-atom systems generally affords a five-membered cyclic cation, which undergoes elimination of an adjacent proton to produce a corresponding cyclic compound. However, the reaction environment can promote [1,2]-migration of adjacent substituent to offer a rearranged cyclic product. This tandem procedure is of significant synthetic importance because it can be employed to create vicinal stereocentres including quaternary centres and latest most attractive protocols dealing with this cascade process are highlighted in this section.

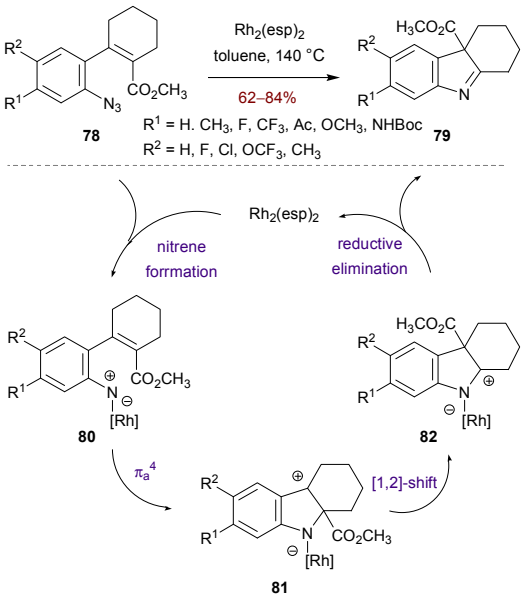
2.2.1 Indoles

Nitrogen containing heterocycles are ubiquitous in natural products of therapeutic value and indoles are one of the privileged motifs of such kind. Recently, Driver and Kong have devised a rhodium$^{(II)}$-catalysed strategy to access 3*H*-indoles from *ortho*-alkenyl substituted aryl azides through a cascade process involving 4π electrocyclisation.[41] Treatment of an aryl azide **78** with sub-stoichiometric amount of rhodium$^{(II)}$ catalyst offers the desired 3*H*-indole **79** (Scheme 11). It is plausible to envisage the formation of *N*-aryl nitrene **80**, triggered by the transition metal catalyst followed by 4π electrocyclisation. A [1,2]-ester migration from the cyclised product **81** affords a heterocyclic intermediate **82** that is converted to the 3*H*-indole substrate on reductive elimination of



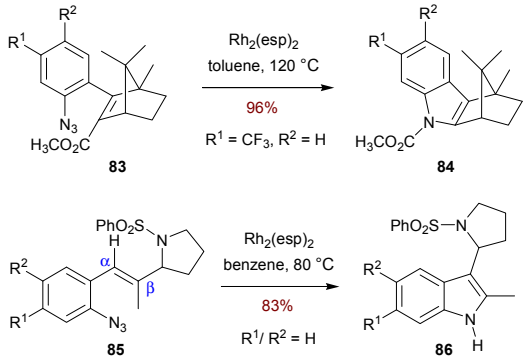
Scheme 10 Regioselective synthesis of indenes **64** and **66** along with DFT corroborated mechanistic investigations for the synthesis of indenes **72** and **75** from aryl alkyne **67**.[40]

the catalyst. The propensity of [1,2]-shift depends on the substituent at β-position of the aryl azide **78**; replacement of the ester with an electron-donating group would follow the ring contraction after electrocyclisation, leading to a spirocyclic product. The methodology works reasonably well with substituents on aryl group (R^1 and R^2), esters other than bearing a methyl group and with different *ortho*-alkenyl substituents.



Scheme 11 Preparation of 3*H*-indoles **79** from styryl azides **78**.[41]

A follow-up work from the laboratory of Driver focuses on the migratory aptitude of ester group during the formation of indole scaffolds from styryl azides.[42] A sterically demanding bicyclic trisubstituted styryl azide **83** with enhanced steric environment around the *ortho*-alkenyl substituent is subjected to the catalytic conditions and, not surprisingly, an indole **84** is formed solely instead of a 3*H*-indole *via* a preferential migration of methyl ester to the nitrogen atom (Scheme 12).[42] Furthermore, it has been demonstrated that aminomethylene group is prone to [1,2]-migration after 4π electrocyclisation in β,β-disubstituted styryl azide **85** to form 2,3-disubstituted indole **86**.[43]

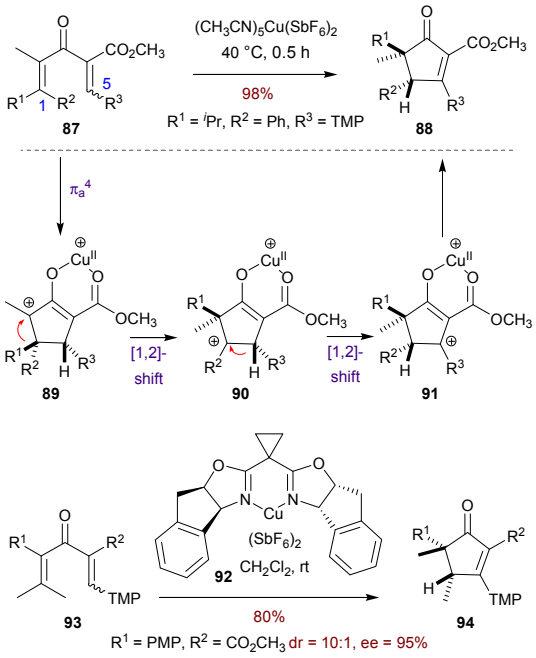


Scheme 12 Domino 4π electrocyclisation–rearrangement strategy to access indoles **84** and **86**.[42,43]

Experiments to validate the proposed mechanism reveals a stepwise migration of the aminomethylene group and migratorial aptitude is found to be in an order of ester << alkyl << aryl << aminomethylene << amide << H << sulfone << ketone << nitro. This catalytic protocol is applicable to a broad range of substrates and can be employed to synthesise indoloazepines.

2.2.2 Cyclopentenones

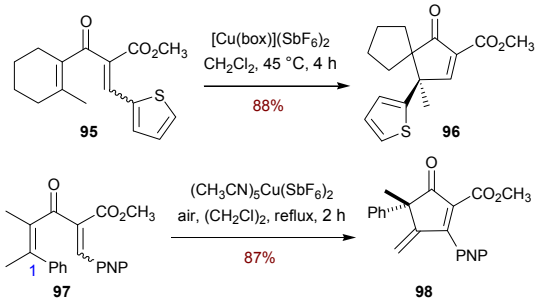
A classical example of 4π-electron-5-atom system is Nazarov cyclisation, which leads to an efficient stereospecific formation of richly substituted cyclopentenone from substituted divinyl ketone and it has particularly been championed by Frontier and co-workers. Based on conrotatory 4π electrocyclisation–Wagner–Meerwein rearrangement cascade, an efficient copper$^{(II)}$-initiated protocol has been developed in her laboratory.[44] The reaction has been studied for an array of divinyl ketones including **87** to gain an efficient access into the corresponding cyclopentenone **88** (Scheme 13).



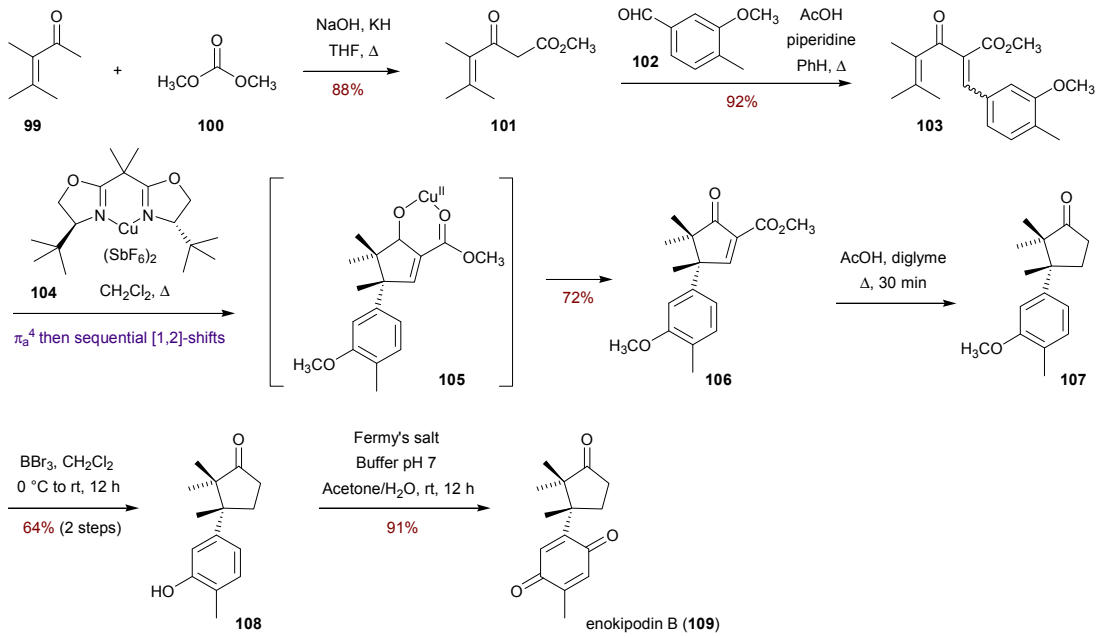
Scheme 13 Stereospecific 4π electrocyclisation–suprafacial Wagner–Meerwein rearrangement cascade towards substituted cyclopentenones **88** and **94**.[44,46]

After initial successful copper$^{(II)}$-triggered electrocyclisation, an oxallyl cationic intermediate **89** is formed that undergoes two different chemoselective sequential [1,2]-suprafacial Wagner–Meerwein shifts to generate the desired product **88** *via* intermediates **90** and **91**. The selectivity of [1,2]-migration is controlled by either electronic or steric effect of the substituents at C-1 and C-5 positions of the starting materials. Interesting findings include i) an increased reaction rate by using TMP group at C-5 position due to steric and electron-donating nature; ii) an *E*/*Z* isomerisation of the enone motif prior to the electrocyclisation under the reaction conditions resulting into a mixture of diastereomeric products. Application of copper$^{(II)}$-bisoxazoline complex makes this route highly diastereoselective by preventing isomerisation of the enone fragment. A catalytic procedure using NaBAr^f as a co-catalyst, comparable to the stoichiometric amounts of copper$^{(II)}$ complex in terms of efficiency and yield, has also been devised. This process is effective for a range of substrates in uniformly high yield and diastereoselectivity. Computational studies performed at an adequate level of theory also corroborate the reported propositions and provide a detailed account towards the migratory aptitude of the substituents during [1,2]-shifts. It has also been demonstrated that the chemoselectivity of this tandem sequence relies on the attached substituents as well as is substantially affected by the ligand structures on the copper$^{(II)}$ promotor.[45] This is applied to establish the carbocyclic framework of several sesquiterpenes from the cuparane and herbertane families of natural products. In the presence of chiral complex **92**, an enantioselective variant of this approach has also been reported to prepare cyclopentenone **94** by employing divinyl ketone **93** (Scheme 13).[46]

In this tandem sequence, the choice of catalyst strongly influence the nature of reaction products as reported for the synthesis of highly functionalised spirocyclic cyclopentenone **96** from the divinyl ketone **95** (Scheme 14).[47] The reaction sequence involves ring contraction followed by a hydride, alkenyl or aryl shift after an initial 4π electrocyclisation–sequential Wagner–Meerwein rearrangement and all steps are highly stereospecific. Despite of excellent yields and mild conditions, the reaction suffers due to stoichiometric amounts of the catalyst and moderate enantiomeric excesses (up to 45%). Extended work from the same group highlights an incorporation of oxidation step to 4π electrocyclisation–Wagner–Meerwein rearrangement. It is a practical way to prepare an exocyclic double bond containing cyclopentenone **98** by treating divinyl ketone **97** with equimolar amount of copper$^{(II)}$ ligand (Scheme 14).[48]



Scheme 14 Frontier's approach to synthesise spirocyclic cyclopentenone **96** and 4-alkylidene cyclopentenone **98**.[47,48]



Scheme 15 4π Electrocyclisation–[1,2]-chemoselective Wagner–Meerwein rearrangement sequence for the synthesis of enokipodin B (**109**).[45]

The method is quite robust and general, applicable to numerous compounds bearing electron-withdrawing aromatic substituents. Presence of steric bulk at C-1 position produces an intricate reaction mixture instead of the desired 4-alkylidine product; presumably it is because of competing rearrangements as the crowdedness offered by a bulky substituent might disfavour oxidation. DFT studies and EPR investigations are in consistent with the experimental results and have been employed to validate the supposition.

Frontier and co-workers have demonstrated a synthetic utility of 4π electrocyclisation–[1,2]-Wagner–Meerwein rearrangement cascade by accomplishing a concise total synthesis of enokipodin B (**109**, scheme 15).[45] Enokipodins belong to to sesquiterpene natural products and have been isolated from an edible mushroom, *Flammalina vellutepes*. These have been reported to exhibit antifungal and antibiotic characteristics. Also, the core cyclopentenone scaffolds bearing contiguous quaternary stereocentres were also synthesised for other related biologically active natural products including β-herbertenol, cuparene, herbertene, infuscol A and δ-cuparenol.

Formation of β-ketoester **101** was realised by alkylation of the enone **99** with dimethylcarbonate **100** (Scheme 15).[45] Knoevenagel condensation of ester **101** with aryl aldehyde **102** furnished substituted divinyl ketone **103** as an *E*/*Z* mixture in an excellent yield. Remarkably, only *cis*-isomer undergoes 4π electrocyclisation–rearrangement sequence in the presence of bulky copper$^{(II)}$ bisoxazoline complex **104** to yield cyclopentenone **106** *via* an intermediate **105**. This domino sequence enables installation of both adjacent quaternary centres present in enokipodin B (**109**).

Removal of carbomethoxy group using NaI/AcOH in diglyme under reflux conditions led to the cyclopentanone **107**. The rest of the synthetic modifications are straightforward comprising of demethylation and subsequent oxidation of the resultant cyclopentanone **108** using Fremy's salt, which complete a total synthesis of enokipodin B (**109**) in six steps with 33.9% overall yield.

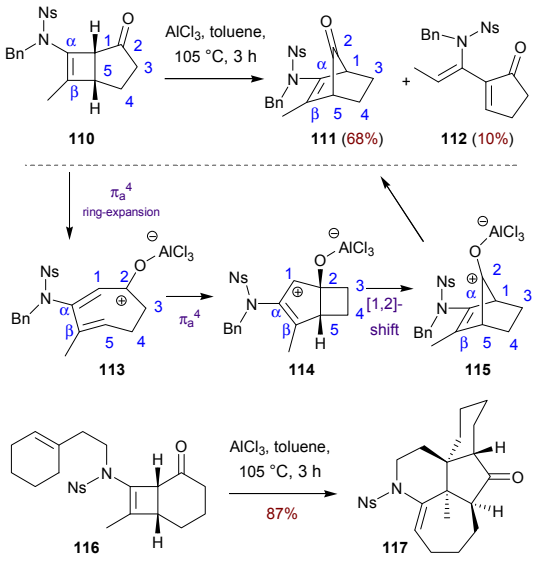
2.3 4π Electrocyclisation in electrocyclisation cascade

Use of electrocyclisation cascade is an impressive approach to install structural complexity towards the synthesis of demandingly challenging substrates from simple and readily accessible starting materials *via* one-pot transformation. This section gives a precise overview for the applications of 4π electrocyclisation in electrocyclisation cascade.

2.3.1 Cyclic ketones

Recently, a scientific collaboration between the research groups of Krenske, Houk and Hsung have produced an impressive work which amplifies the synthetic applicability of 4π electrocyclic reactions in a cascade. Based on an extensive theoretical and experimental studies, aluminium$^{(III)}$ chloride-promoted formation of carbocyclic ketone **111** from bicyclic cyclobutenamide **110** is reported (Scheme 16).[49] Initially, *Z*,*E*-cycloheptadienone **113** is formed as a result of a torquoselective 4π electrocyclic ring-expansion followed by conrotatory 4π electrocyclic ring-closure to generate an intermediate **114**. At this juncture, [1,2]-alkyl shift leads to bicyclic structure **115**, which terminates into the desired ketone **111** along with cyclopentenone **112** as a minor product. The reaction is applicable to several cyclobutenamides and in each case, formation of 2-amidodiene **112** is observed as an exclusive *cis*-isomer. In

addition to this, tri- and tetracyclic products have been achieved in an efficient manner using this methodology. For instance tetracyclic compound **117** can be prepared in an excellent yield by using 4,6-fused cyclobutenamide **116**. In this case, 4π electrocyclic cascade is followed by Prins-like cyclisation of the tethered alkene onto bicyclic intermediate similar to **115**, [1,2]-alkyl shift and retro-aldo ring-opening to furnish the tetracyclic scaffold **117** as a single reaction product. The absolute structures of the products have been unambiguously confirmed by single-crystal X-ray analysis.

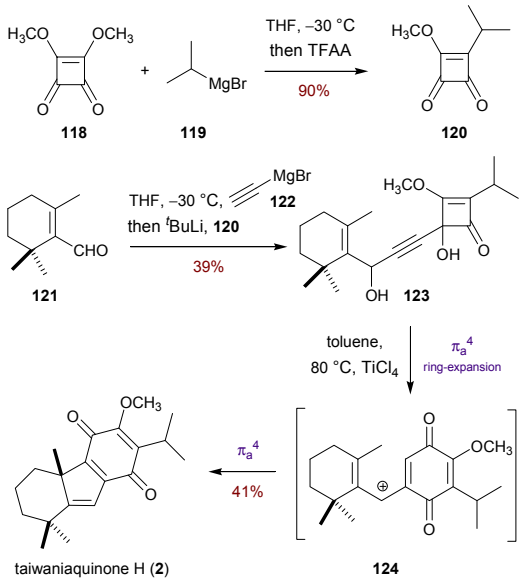


Scheme 16 Synthesis of cyclic ketones **111** and **117** from cyclobutenamides **110** and **116** respectively; application of 4π electrocyclisation cascade.[49]

2.3.2 Taiwaniaquinoids

Hu and Yan employed a thermal 4π ring-opening–4π electrocyclisation strategy to influence a direct and complete atom economical formation of stereodefined core tricyclic unit of taiwaniaquinone H (**2**) in a moderate yield form cyclobutenone **123** (Scheme 17).[4] The reaction works smoothly, if carried out stepwise however one-pot synthesis has been achieved using titanium$^{(IV)}$ chloride as a Lewis acid to promote the 4π electrocyclic ring-closure. The key domino transformation enables to evade cumbersome multistep transformations towards the synthesis of core carbocyclic skeleton, which is a distinguished structural feature for a large number of natural products belonging to terpenoid family, taiwaniaquinoids. These compounds exhibit promising cytotoxicity and possess unusual structural skeleton.

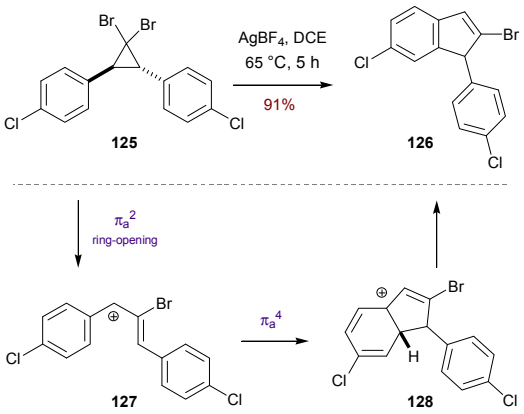
The reported route is an excellent example of convergent synthesis and commences with an efficient preparation of cyclobutenedione **120** by alkylation of dimethyl squarate **118** with isopropyl magnesium bromide **119** (Scheme 17).[4] This addition provides an earlier installation of the isopropyl group present in the natural product **2**. On the other hand, treatment of readily available aldehyde **121** with ethynyl magnesium bromide **122** furnished corresponding alkyne, which was deprotonated and cyclobutenedione **120** was added to the same reaction mixture. This one-pot strategy gives an immediate access to the cyclobutenone **123**, despite the yield being low. No improvement in the yield of cyclobutenone **123** was observed even by performing the reaction in two separate steps. A domino reaction involving thermal conrotatory ring-opening followed by 4π electrocyclisation in hot toluene resulted in the total synthesis of taiwaniaquinone H (**2**) from cyclobutenone **123** *via* pentadienyl cation **124**. This route demonstrates a total synthesis of a structurally demanding natural product in three steps from commercially available starting materials with 14% overall yield.



Scheme 17 Hu's succinct route to taiwaniaquinone H (**2**); application of thermal ring expansion–4π electrocyclisation sequence.[4]

2.3.3 Bromoindenes

2-Bromoindenes are valuable synthetic blocks with enormous applications in several transition-metal controlled cross-coupling strategies. An unconventional approach to prepare these motifs has been devised by Batey and Rosocha. They have investigated a silver$^{(I)}$-catalysed 2π disrotatory electrocyclic ring-opening of gem-dibromocyclopropanes and found that this process can be effectively combined with 4π conrotatory electrocyclic ring-closure to prepare 2-bromo-1-aryl substituted indenes.[50] A domino pathway involves ionisation–2π disrotatory electrocyclic ring-opening of symmetrical gem-dibromocyclopropane **125** to yield a pentadienyl cation **127**, which subsequently undergoes 4π electrocyclic ring-closure to generate 2-bromoindene **126** *via* an intermediate **128** (Scheme 18). With unsymmetrical cyclopropanes, the reaction suffers selectivity issues at electrocyclic ring-opening stage and a mixture of products are obtained, though in good to excellent yields.



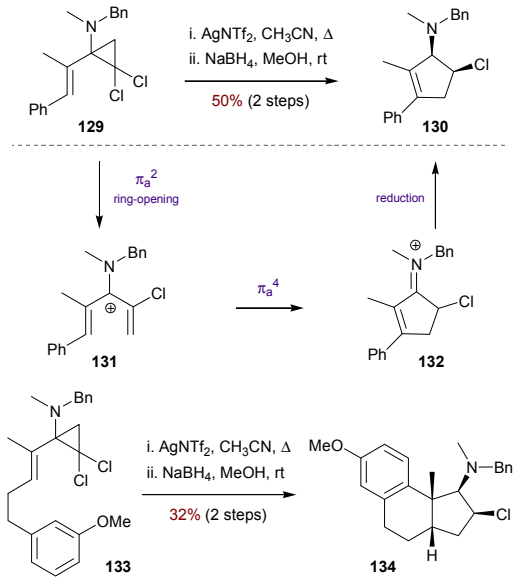
Scheme 18 Synthesis of bromoindene **126** *via* 2π–4π electrocyclisation sequence.[50]

2.3.4 Cyclic Amines

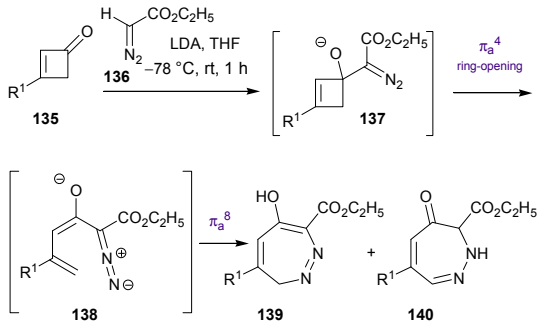
It has been found that gem-dichlorocyclopropane **129** undergoes ring-opening followed by 4π electrocyclisation to construct cyclopentenone iminium salt **132** through a Nazarov-type cyclisation of aminopentadienyl cation **131** (Scheme 19).[51] Reduction of the resultant iminium salt using a conventional hydride source provides allylic amine substrate **130**. Further investigations reveal that an addition of one equivalent of a Brønsted acid adversely affect the ring-opening of cyclopropanes due to protonation of nitrogen group however ring-opening is facilitated by the presence of electron-rich amino groups. In addition to this, the domino sequence consisting of 2π–4π electrocyclisation cascade applied to functionalised cyclopropane **133** is combined with arene trapping after successful imino-Nazarov cyclisation that further undergoes reduction to finally afford a tricyclic product **134** as a single isolated product. The reaction produces two diastereomeric compounds (dr 1.2:1) confirmed by the crude mixture, however the major isomer is decomposed by silica gel during chromatographic purification.

2.3.5 1,2-Diazepines

Diazepines containing natural and synthetic compounds have found particular applications in medicinal chemistry and several elegant approaches involving pericyclic reactions to prepare such scaffolds have been identified. Matsuya and co-workers have reported a formal diazomethylene insertion reaction into the C–C bond of cyclobutenone to access unannulated monocyclic 1,2-diazepines.[52] Treatment of cyclobutenone **135** with an excess of ethyllithiodiazoacetate generated from a diazo species **136** provides an intermediate **137** (Scheme 20). Successive 4π–8π electrocyclisation protocol furnishes a tautomeric mixture of diazepines **139** and **140** *via* geometrically fixed diazo-diene **138**.



Scheme 19 2π–4π electrocyclisation process followed by hydride reduction to prepare cyclic amines **130** and **134**.[51]



R^1	139:140	yield (%)
Ph	86:14	84
4-F-C_6H_4	90:10	71
1-naphthyl	72:28	78
2-CH_3-C_6H_4	73:27	77
^{n}Bu	88:12	64

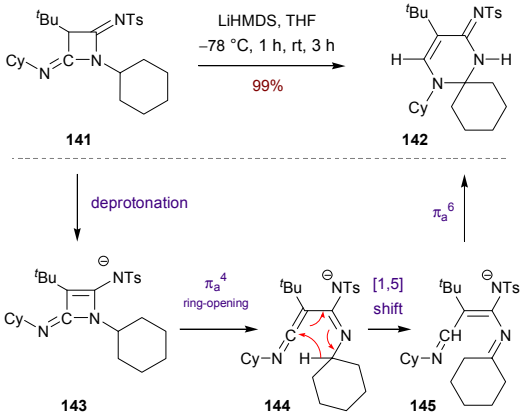
Scheme 20 Formation of monocyclic 1,2-diazepines **139** and **140** through tandem 4π–8π electrocyclisation route.[52]

Careful choice of reaction conditions encourages isomerisation of diazepine **139** into its tautomer **140**, which is found to be more stable. This led to design a dual reaction manifold that permits a selective synthesis of both tautomers in an efficient manner. Notably, mild reaction conditions significantly influences the suppression of nitrogen extrusion, in the absence of thermal

activation. Also, oxy anion in the intermediate **137** fully controls torquoselective 4π electrocyclic ring-opening and directs the orientation of diazo group in the intermediate **138**, which leads to 8π electrocyclic ring-closure.

2.3.6 2,3-Dihydropyrimidinesulfonamides

Research groups of Zhang and Xi have used electrocyclisation cascade as a means to amplify the practicality of tandem pericyclic reactions involving 4π electrocyclisation.[53] They have demonstrated very first examples of spiro-2,3-dihydropyrimidinesulfonamides such as **142** directly obtained from 2,4-diminoazetidine **141** bearing a cyclohexyl group attached to the nitrogen atom of the azetidine in an excellent yield (Scheme 21). After initial deprotonation, highly regioselective cleavage of C–N bond takes place in the resultant intermediate **143**, which ring-opens through a 4π electrocyclic process to give an intermediate **144**. Presumably, regioselective alkylimino C–N bond cleavage over sulfonylimino C–N bond occurs due to presence of a weak bond of alkylimino C–N bond. Because of an inherent electron-withdrawing nature, sulfonyl group influences to decrease the bond length of sulfonylimino C–N, which results a stronger sulfonylimino C–N bond. A [1,5]-H shift leads to the intermediate **145** that follows a predictable 6π electrocyclic pathway to furnish spirocyclic compound **142**. The mechanistic proposal is backed by trapping experiments of key intermediates and deuterium labelling studies. The reaction is well-tolerated by variously substituted aromatic rings as well as a broad range of functional groups in uniformly high yields and regioselectivity.



Scheme 21 Towards spiro-2,3-dihydropyrimidinesulfonamide **142** from 2,4-diminoazetidine **141** *via* 4π ring-opening–6π electrocyclisation protocol.[53]

2.4 Synthetic transformation–4π electrocyclisation sequence

Several conventional reaction protocols provide suitable substrates, which are amenable to 4π electrocyclisation. Recent examples are listed in this section that involve a well-known transformation prior to 4π electrocyclisation in a domino process.

2.4.1 5-Hydroxycyclopentenones

Frontier and colleagues envisaged the possibility of developing a Lewis acid-assisted tandem sequence comprising of 1,6-nucleophilic conjugate addition and 4π electrocyclisation.[54-56] They found that acetate tethered containing dienyl diketone **146** and **148** follow two different 1,6-conjugate addition-promoted cyclisation cascades and generate corresponding products **147** and **149** respectively (Scheme 22).[55,56] Lithium chloride and triethylamine have substantial impact on the solubility of the catalyst. A wide range of nucleophiles including primary amines, cyclic and acyclic secondary amines, malonate derivatives can be employed as external nucleophiles and more importantly, a single diastereomeric product is achieved in all cases. Interestingly, use of dimethylamino pyridine (DMAP) as a nucleophile provides dienone instead of regular enone products.

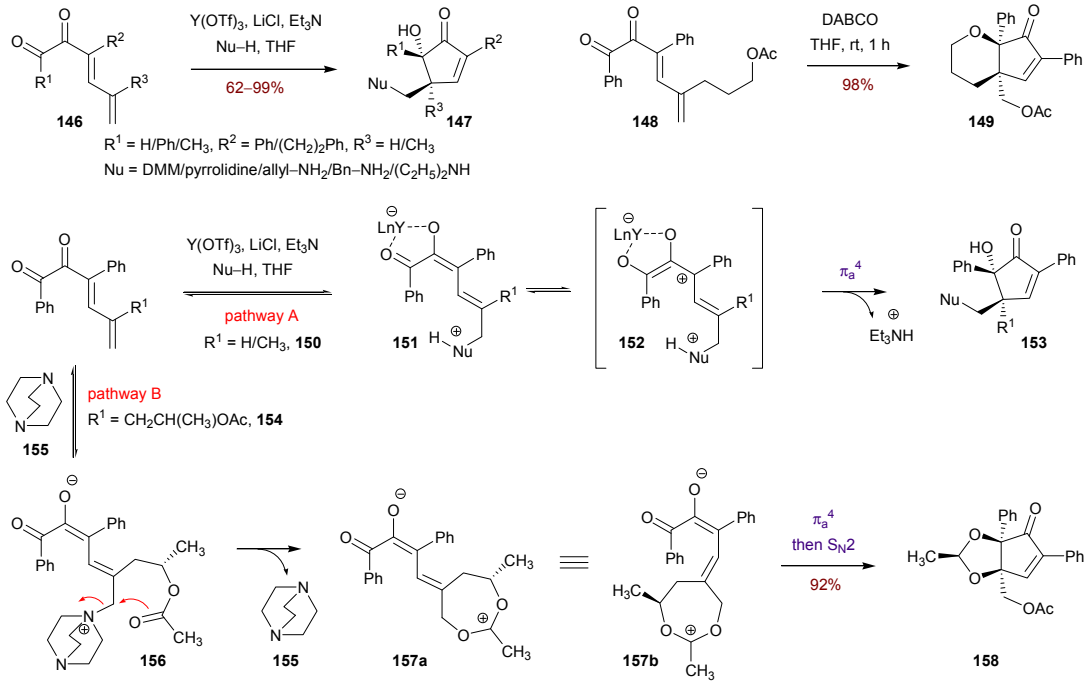
Nucleophilic addition of pyrrolidine or dimethylmalonate to dienyl diketone **150** leads to a conventional 1,6-addition and an adduct **151** is formed (pathway A, scheme 22).[55] Isomerisation and bond rotation of intermediate **151** furnishes the corresponding cationic intermediate **152**, which undergoes regiospecific conrotatory 4π cyclisation to give richly functionalised 5-hydroxycyclopentenone **153**. This cascade is of great synthetic interest because of installation of all-carbon quaternary and contiguous tertiary stereogenic centres in an efficiently stereospecific manner. However, use of DABCO **155** as an external nucleophile with dienyl diketone **154** offers a zwitterionic DABCO adduct **156** (pathway B, scheme 22).[55] At this stage, pendant acetate group displaces the allylic quaternary ammonium motif to give another zwitterionic compound **157a**, amenable to bond rotation to offer an equivalent cyclic structure **157b**. The inscribed stereocentre in the intermediate **157b** controls torquoselective 4π electrocyclisation followed by an intramolecular S_N2 to end up into the desired enone **158**. Additionally, this zwitterion containg cyclisation strategy (pathway B) is applicable to a range of substrates *via* seven-, eight-, and nine-membered zwitterionic intermediates.

At times, interesting and unexpected results warrant further investigation that evolves new arenas of research. Li and co-workers have demonstrated that dioxolanone **159** smoothly undergoes a hydride reduction to form 5-hydroxycyclopentenone **161** *via* 4π electrocyclisation (Scheme 23).[8] The reaction is believed to proceed through tethered 1,2-oxidopentadienyl cation species **160a**, which readily isomerises to a resonance hybrid structure **160b**. The generality of reaction is explained by a stereospecific formation of an array of 5-hydroxycyclopentenones including spiro-cyclopentenone and quaternary carbon containing product. Asymmetric variant of hydride reduction–4π electrocyclisation tandem sequence reveals a moderate level of diastereoinduction (dr 5:1) when applied to a chiral dioxolanone.

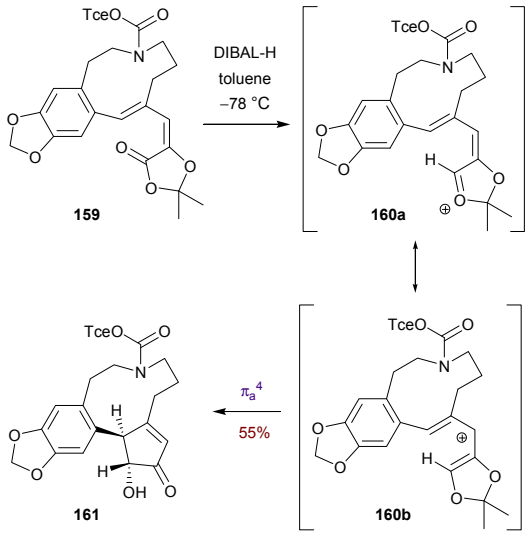
Based on hydride reduction–4π electrocyclisation domino process, a transannulation strategy has been employed to achieve the total synthesis of (±)-cephalotaxine (**6**), which is a core structural motif for *cephalotexus* alkaloids.[8] The family of these natural products possess anti-leukemic activity and have been interesting synthetic targets for the scientific community. Construction of annulated

product **164** bearing aldehyde moiety was achieved by the condensation of norhydrastinine (**162**) with iodo enolsilane **163** (Scheme 24).[8] The aldehyde **164** was treated with superstoichiometric amounts of 2,2,2-trichloroethyl chloroformate to provide macrocyclic aldehyde **165** in an excellent yield. Wittig olefination of the aldehyde **165** with dioxolanone **166** afforded *E*-dioxolanone **159**, which underwent the key tandem reaction sequence through the pentadienyl cation **160b** to furnish the desired 5- hydroxycyclopentenone **161** in a stereospecific manner.

Acetylation of incipient hydroxyl group followed by selective cleavage of *N*-Troc group yielded a transannular cyclisation product **167** that was subsequently oxidised to demethylcephalotaxinone (**168**). The end-game was achieved by employing previously established three-step protocol entailing methylation, optical resolution with L-tartaric acid and borohydride reduction to accomplish a successful total synthesis of (±)-cephalotaxine (**6**) in nine steps from readily available starting materials.



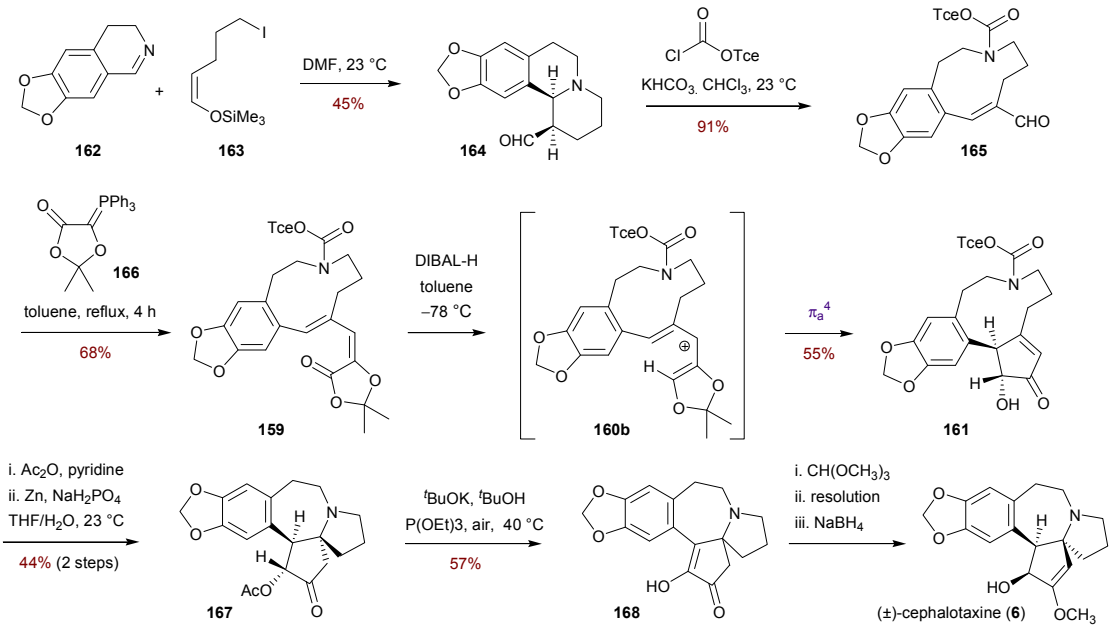
Scheme 22 Nucleophilic conjugate addition followed by 4π electrocyclisation to prepare cyclopentenones **147**, **149**, **153** and **158**.[55,56]



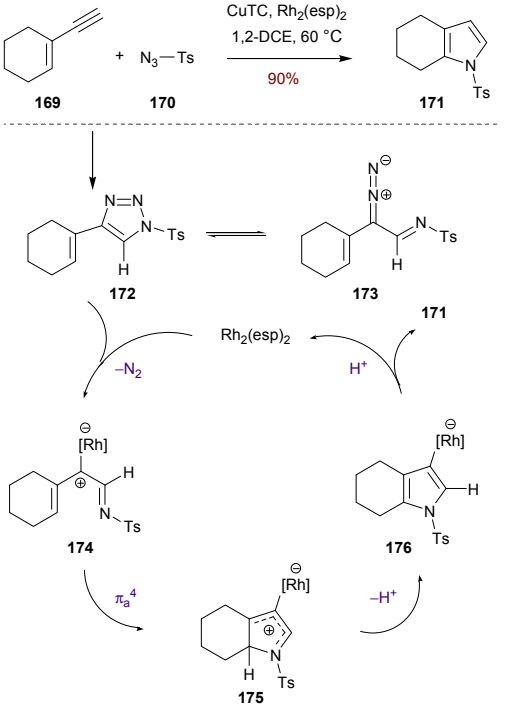
Scheme 23 Hydride reduction–4π electrocyclisation to obtain 5-hydroxycyclopentenone **161** from dioxolanone **159**.[8]

2.4.2 Pyrroles

Research work from the laboratory of Davies demonstrates an efficient synthesis of 2,3-fused pyrroles from cyclic enyne derivative.[25] This dirhodium-mediated one-pot strategy is based on the treatment of cyclohexenylalkyne **169** with tosyl azide **170** to form a 1,2,3-triazole **172** (Scheme 25). Under thermal activation, ring–chain isomerisation followed by nitrogen extrusion *via* isomerised species **173** takes place to afford rhodium-stabilised iminocarbene intermediate **174**, which on 4π electrocyclisation gives pyrrolylium cation **175**. Subsequent proton elimination and aromatisation furnishes a vinylrhodium motif **176** that on exposure to acidic environment provides the desired pyrrole **171** in an excellent yield. The reaction finds its applications to construct steroid skeletons of 5-cholestan-3-one and nootkatone, and presence of heteroatoms in the cyclohexenyl ring is well-tolerated. Remarkably, the reactions works effectively with a sequential DDQ oxidation after cyclisation to generate several substituted indoles and azaindole.



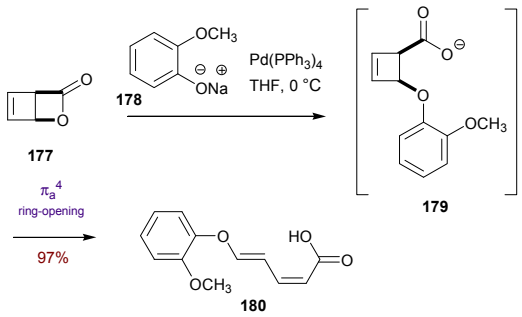
Scheme 24 Li's synthetic strategy for (±)-cephalotaxine (**6**); domino reaction involving reduction–4π electrocyclisation cascade.[8]



Scheme 25 An efficient one-pot synthesis of pyrrole **171** by the reaction of cyclohexenylalkyne **169** with tosyl azide **170**.[25]

2.4.3 Dienes

Maulide and co-workers have reported a stereoselective preparation of functionalised, geometrically defined uncommon *Z,E*-dienes such as **180** by nucleophilic attack of sodium salt of substituted phenol **178** onto lactone **177** followed by 4π electrocyclic ring-opening of the resultant cyclobutene **179** (Scheme 26).[14] The reaction is strictly regulated by palladium catalyst as no product is observed in its absence. Alkyl or aryl substituted lactones and an array of phenols act as good external nucleophiles to afford the corresponding *Z,E*-5-aryloxydienyl carboxylic acids. Astonishingly, strongly electronically deactivated pentafluorophenol can also participate as an efficient nucleophile. The structural assignments are unequivocally confirmed by single-crystal X-ray analysis.

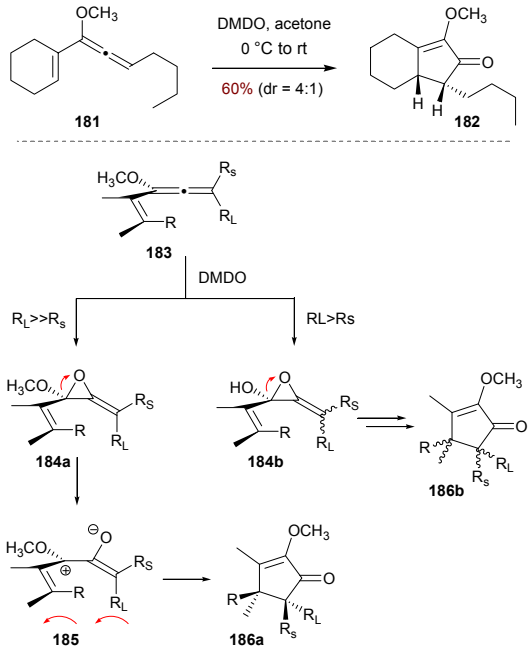


Scheme 26 Stereoselective preparation of functionalised diene **180** *via* domino allylic alkylation–4π electrocyclic ring-opening.[14]

2.4.4 Alkoxycyclopentenones

Research group of Frontier have studied the oxidation of cyclohexenyl allene **181** to provide an exclusively *cis*-selective bicyclic cyclopentenone **182** (Scheme 27).[57] Use of DMDO as an oxidising agent furnishes the corresponding product in 4:1 diastereomeric ratio however, replacement with a bulky oxaziridine improves diastereoselectivity (up to 8:1) in comparatively lower yield (48%). The stereochemical outcome suggests that the oxidation takes place on the face of the electron-rich internal

alkene double bond of allene, away from the terminal substituent. The obtained diastereoselectivity is rationalised on the basis of steric bulk of two substituents on the allene terminus of the cyclohexynyl allene **183**. A substantial difference between the two substituents on the allene terminus results in DMDO oxidation of the allene moiety on the face opposite to the R_L. This gives rise to either allene oxide **184a** as a single diastereomer or a pentadienyl cation **185** from allene oxide **184a**, which generates single diastereomer of cyclopentenone **186a** through conrotatory 4π electrocyclic ring-closure. However, for the substrates with smaller steric difference between the two substituents on the allene terminus, the oxidation step is not regiospecific and a mixture of cyclopentenone **186b** is produced *via* allene oxidised product **184b**.



Scheme 27 Oxidation–4π electrocyclization route to access alkoxycyclopentenones **182**, **186a** and **186b**.[57]

Research executed in the laboratory of Frontier displays a linear synthetic approach towards the total synthesis of (±)-aglafolin (**202**), (±)-rocagloic acid (**203**) and (±)-rocaglamide (**4**), which are few of the potent natural products isolated from *Aglaia elliptifolia* and exhibit remarkable biological activity including insecticidal, anti-inflammatory and anticancer.[6a] These bioactive compounds are characterised by the occurrence of cyclopenta[*b*]benzofuran scaffold, readily achievable by synthetic manipulations of cyclopentenone, which is directly obtained by employing an oxidation–4π conrotatory electrocyclic ring-closure cascade. Utilisation of Hoesch reaction applied to phloroglucinol (**187**) and cyanohydrin **188** furnished the corresponding diphenolic benzofuranone, which underwent methylation of free hydroxyl group to give dimethylated benzofuranone **189**, despite of yield being very low over two steps (Scheme 28).[6a] Addition of vinyl magnesium bromide **190** to benzofuranone **189** yielded 3-vinylbenzofuranone **191** with an elimination of water molecule. A quantitative oxidative cleavage generated the aldehyde **192** that was treated with lithiated phenylacetylene **193** to afford propargylic alcohol **194**. From this, a propargylic ether **195** was prepared by *O*-alkylation which was subsequently converted to alkoxyallene **196** in an efficient manner. A tandem oxidation–4π electrocyclisation sequence was applied to allene **196** to generate cyclopentenone **198** as a single diastereomer *via* pentadienyl cation **197**. At this juncture, a dual action strategy was employed involving DDQ oxidation of cyclopentenone **198**, which resulted in cleavage of PMB group as well as oxidation at carbon 8b to furnish diosphenol **199**. Standard conditions for triflate formation followed by palladium-catalysed carbonylation in methanol provided alkylidene β-ketoester **201** through the triflate **200**. With this, installation of the carbon skeleton present in the natural products was achieved. Hydrogenation of ester **201** followed by sodium triacetoxyborohydride reduction gave (±)-aglafolin (**202**) as a single diastereoisomer. Then, base-promoted saponification afforded (±)-rocagloic acid (**203**), which was finally converted to (±)-rocaglamide (**4**) by dicyclohexyl carbodiimide-mediated amide coupling.

2.4.5 Cyclopentadienes

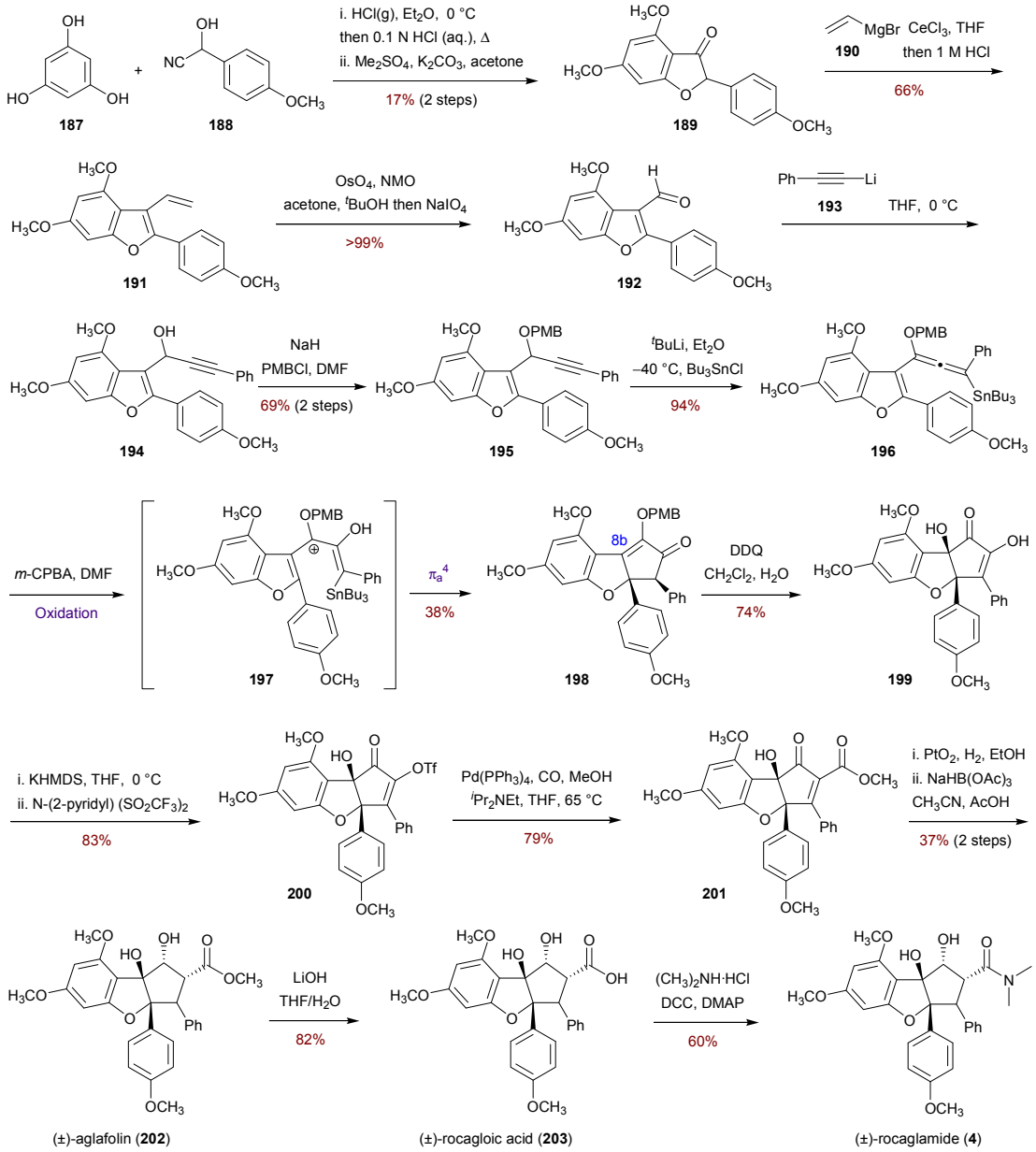
Liang and colleagues have designed a palladium-catalysed transformation of *Z*-2-en-4-yn acetate **204** with *N*-methyl indole (**205**) to access tetrasubstituted cyclopentadiene **206** (Scheme 29).[58] The substrate scope of this reaction is broad and the desired products are formed using mild reaction conditions however, it fails to respond in the presence of Lewis acids. This one-pot reaction sequence can also be extended to access halogen substituted cyclopentadienes by employing copper$^{(II)}$ chloride or bromide as a nucleophile, albeit in low yield (up to 46%). After initial attack of indole **205** to acetate **204**, a Fridel–Crafts arylation product **207** is generated that undergoes 6-*endo-dig* cyclisation to form a spirocyclic intermediate **208** *via* activation of C–C triple bond by the catalyst. Migration of C–C double bond results into pentadienyl cation **209**, which is set for 4π electrocyclisation to afford palladium-carbene intermediate **210**. At this stage, [1,2]-indole migration with reductive elimination of the catalyst provides cyclopentadiene **211**, which isomerises to the desired product **206**.

2.5 4π Electrocyclisation–synthetic transformation process

4π Electrocyclisation followed by a synthetic transformation is an elegant approach to add desired functionalities in a molecule and recent examples from this area of research are illustrated in this section.

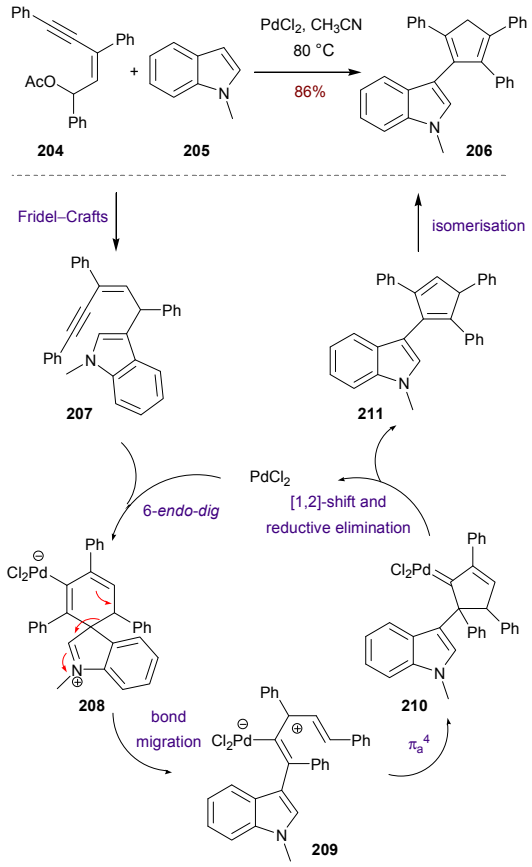
2.5.1 Cyclopentanones

West and Wu envisioned the reaction of cross-conjugated ketone **212** with aryl acetylene **213** to form an α-phenacyl cyclopentanone **214** in highly regio- and stereoselective fashion (Scheme 30).[59]

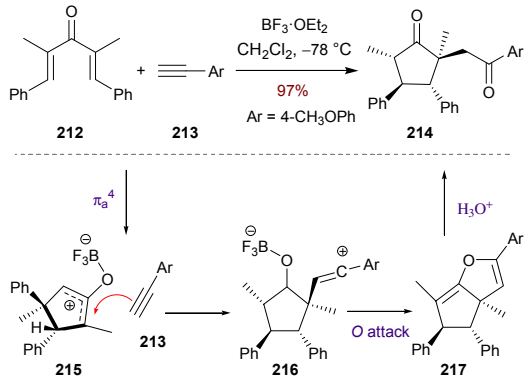


Scheme 28 Frontier's approach towards (±)-aglafolin (**202**), (±)-rocagloic acid (**203**) and (±)-rocaglamide (**4**); synthetic utility of oxidation–4π electrocyclisation tandem reaction.[6a]

The transformation is catalysed by BF_3- etherate and a convenient availability of starting material imply that a broad range of substituents can be added to the reaction products. Alkyl and silyl substituted alkynes result in complete utilisation of the dienone partner without giving any desired products however, an array of functionalised aryl substituted alkynes are compatible nucleophilic enol surrogates. After 4π electrocyclisation, cyclopentenyl cation **215** is formed, which is successfully trapped by an addition of aryl alkyne **213**. An *anti* approach of the alkyne to the adjacent phenyl group leads to the formation of vinyl cation **216** that undergoes an intramolecular oxygen-mediated cyclisation to afford a strained dihydrofuran **217**. Then, the anticipated cyclopentenone **214** is furnished through aqueous work-up. Notably, bridged bicyclic compound is not observed; a possible product as a result of a formal [3+2] cycloaddition between aryl alkyne **213** and cyclopentenyl cation **215**. Incorporation of 4-vinylanisole instead of aryl alkynes as nucleophilic partner assist the formation of aryl substituted bicyclic ketone as a single diastereome, albeit in low yield (33%). Overall, the transformation is high yielding, stereospecific, installs two new C–C bonds, four new sterocentres and provides an expedient access to densely functionalised cyclopentenones with an added carbonyl functionality.

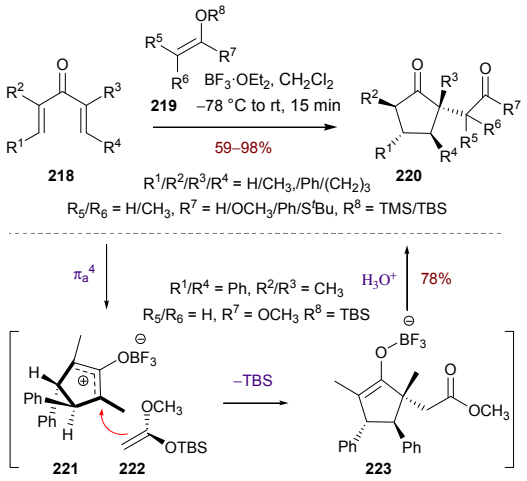


Scheme 29 Fridel–Crafts arylation–[1,5]-indole shift–4π electrocyclisation–[1,2]-indole migration sequence towards the synthesis of tetrasubstituted cyclopentadiene **206**.[58]



Scheme 30 4π electrocyclisation followed by nucleophilic addition to generate cyclopentanone **214**.[59]

Another related approach towards an efficient generation of cyclopentenone **220** as a single diastereomer has been developed in the laboratory of West, which entails treatment of pentadienone **218** with electron-rich siloxyalkene **219** as oxygenated π–nucleophile (Scheme 31).[60] The reaction is tolerant to a variety of richly substituted divinyl ketones along with silyl enol ethers, silyl ketene acetals and mixed ketene *S*,*O*-acetals. The reaction pathway proceeds through cyclopentenyl cation **221**, which is attacked by a siloxyalkene **222** *anti* to the β-phenyl substitution of the cationic intermediate. It provides a quaternary stereocentre in in the resultant intermediate **223** with an extrusion of the silyl group. The corresponding cyclopentenone is generated after highly stereoselective protonation. Remarkably, the sequence also exhibits an excellent stereocontrol at the only exocyclic stereocentre leading to an installation of five stereogenic centres in a single reaction.



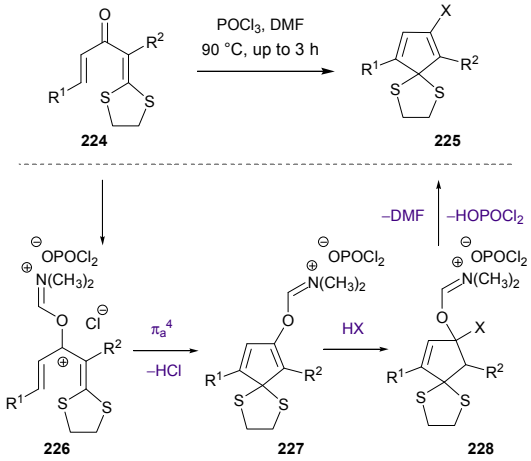
Scheme 31 Domino sequence entailing 4π electrocyclisation–nucleophilic addition to prepare cyclopentanone **220**.[60]

2.5.2 Cyclopentadienes

A novel Vilsmeier reagent based activation mode for divinyl ketone substrates towards 4π electrocyclisation has been studied by Wang and colleagues. Exposure of dithioacetal **224** to Vilsmeier reagent smoothly furnishes pentadienyl cation **226**, which undergoes electrocyclisation to form enol intermediate **227** after elimination of hydrogen chloride (Scheme 32).[61] Then, an addition of hydrochloric or hydrobromic acid generates an intermediate **228** that on elimination of DMF gives halogenated cyclopentadiene **225**. The methodology has certain advantages including facile reaction conditions, broad scope, uniformly high yields and application of conveniently accessible starting materials. Furthermore, halo-substituted cyclopentadienes are equivalent to cyclopentadienone, an important 4π electron templates and have been strategically employed to an efficient [4+2] cycloaddition in combination with dimethyl-2-butynedioate to access polyaryls in a regiospecific fashion.

2.6 4π Electrocyclisation–cyclisation methodology

Cyclopentenyl cations formed as a result of 4π electrocyclisation are important intermediates with enormous synthetic potential and can be trapped by several cyclisation pathways including pericyclic reactions. Also, 4π electrocyclic ring-opening is a conventional approach to generate stereodefined dienes, which can undergo Diels–Alder cycloaddition with a suitable dienophile. This section



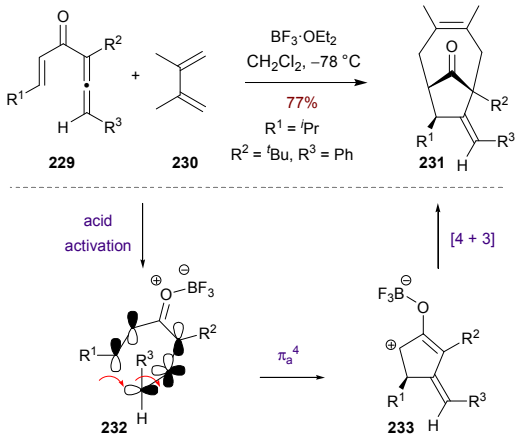
R^1	R^2	X	yield (%)
4-$CH_3OC_6H_4$	Ph	Cl	86
4-$CH_3OC_6H_4$	4-biphenyl	Cl	80
4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	Br	84
2-$CH_3OC_6H_4$	4-FC_6H_4	Br	85
CH_3	Ph	Br	80

Scheme 32 4π electrocyclisation–halovinylation approach for the synthesis of cyclopentadiene **225**.[61]

delineates the merits of such protocols which have recently been incorporated into existing literature.

2.6.1 Bicyclic ketones

Allenyl vinyl ketones with the allenes bearing axial chirality are significant structures and have been subjected to 4π electrocyclisation to produce corresponding cyclopentenones having exocyclic alkene with *cis*-geometry. Lately, an interesting application of allenyl vinyl ketone to prepare bicyclic ketones in a domino process has been demonstrated by the research groups of Boyd and Burnell.[20] Activation of allenyl vinyl ketone **229** by boron trifluoride diethyl etherate provides an intermediate species **232**, which determines the geometry of incipient exocyclic alkene *via* bond rotation and torquoselectivity of 4π electrocyclisation (Scheme 33). An outward rotation in which the substituents on the allene terminus rotate away from the vinyl moiety leads to cyclopentenyl cation **233** which is effectively intercepted by butadiene **230** to provide bicyclic ketone **231** in a highly diastereoselective manner (dr > 20:1). NOE experiments validate that the reaction pathway *via* outward rotation of the substituents on the allene terminus during 4π electrocyclisation followed by [4+3]-cyclisation has occurred onto the cation **233** on the face opposite to the R^1 substituent. As anticipated, an increase in the size of R^1 substituent enhances the torquoselectivity and substitution on the allene motif substantially decreases the yield of the reaction in comparison with the unsubstituted allene. A thorough computational studies reveal a kinetic preference for the observed isomer and torquoselectivity of 4π electrocyclisation is significantly controlled by steric interactions and degree of allene deformation.



Scheme 33 4π electrocyclisation–[4+3]-cyclisation cascade towards bicyclic ketone **231**.[20]

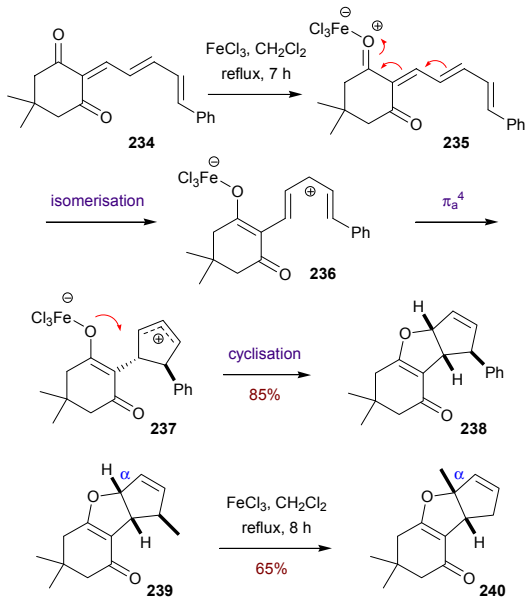
2.6.2 Cyclopenta[*b*]furan Derivatives

Cycloisomerisation is a phenomenal approach to build polycyclic compounds in a single operation. Mischne and Riveira came up with a plan to accomplish cyclopentannulation of linearly conjugated 1,3-dicarbonyl substrate **234** (Scheme 34).[62] An iron$^{(III)}$-mediated catalysis provides a corresponding species **235**, which readily isomerises to pentadienyl cation **236**. Then, 4π electrocyclisation furnishes cyclopentenyl cation **237** that may receive intramolecular stabilisation by a through-space interaction with the π electrons of the enoyl moiety. Trapping of the cation **237** by enolic oxygen provides an exclusive formation of *cis*-fused cyclopenta[*b*]furan scaffold **238**. Mechanistic postulation is verified by extensive deuterium-labelling studies and the reaction works equally well with hydrated catalyst and nondried solvent. Five membered dicarbonyl compounds and trienediones bearing two substituents at the end of the polyene chain fail to provide the desired products. In addition to this, treatment of tricyclic product **239** with the catalyst (2 eq.) affords a rearranged cyclopenta[*b*]furan product **240** (Scheme 34).[62] This suggests that the reaction has kinetic and thermodynamic preferences which can lead to two different types of cyclopenta[*b*]furan derivatives.

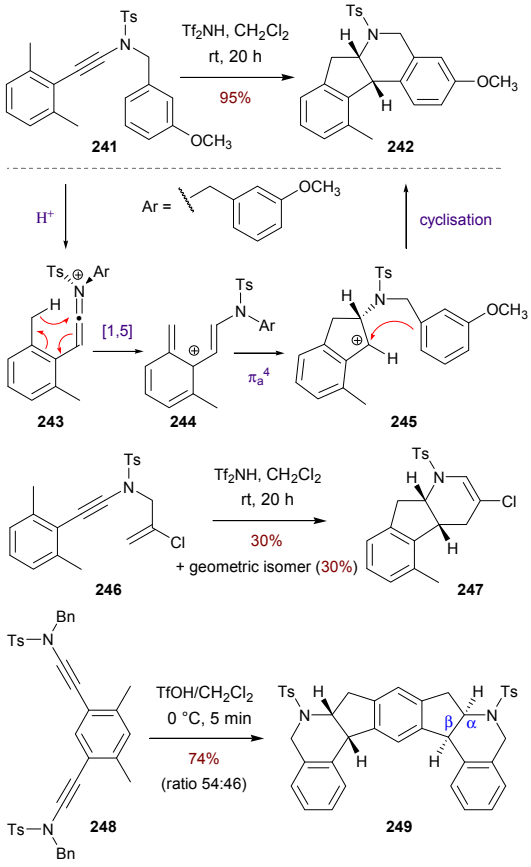
2.6.3 Isoquinoline and Pyridine Derivatives

Inspired by the biomimetic synthesis of steroids and alkaloids, a research collaboration between the groups of Thibaudeau and Evano have produced a cationic polycyclisation cascade to prepare

polycyclic nitrogen heterocycles owning up to seven fused cycles and three contiguous stereocentres.[63]



Scheme 34 An acid-mediated 4π electrocyclisation–cyclisation strategy to cyclopenta[*b*]furan scaffolds **238** and **240**.[62]

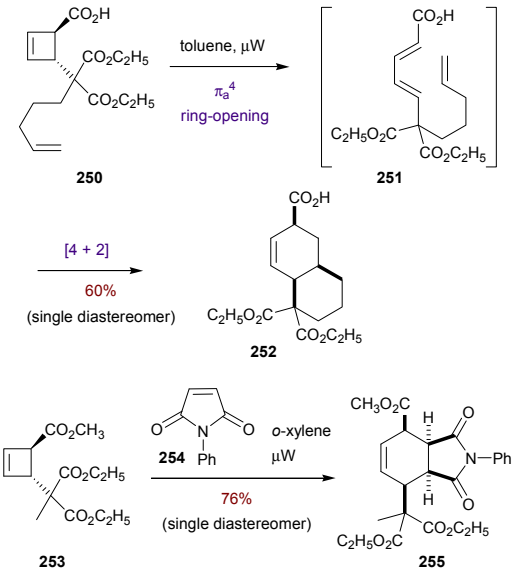


Scheme 35 Polycyclisation in cascade involving 4π electrocyclisation to prepare nitrogen heterocycles **242**, **247** and **249**.[63]

Treatment of *N*-benzyl-ynamide **241** with sub-stoichiometric amounts of bistriflimide affords polycyclised product **242** in an excellent yield (Scheme 35). The reaction is triggered by protonation of the alkyne motif in the ynamide **241** to give highly reactive *N*-tosyl-keteniminium ion **243**, which undergoes [1,5]-hydrogen shift to generate bis-allylic carbocation **244**. At this, 4π electrocyclisation followed by a subsequent intramolecular cyclisation between the intermediate benzylic cation **245** and arene subunit yields the desired *cis*-ring fused nitrogen containing polycyclic compound **242**. In addition to this, the reaction sequence can be applied to a ynamide **246** bearing functionalised alkene as the terminal nucleophile to access tricyclic indenotetrahydropyridine **247**. The transformation is also amenable to double polycyclisation from bis-ynamide **248** to prepare heptacyclic nitrogen heterocycle **249** in almost equal amount of diastereomers with opposite stereochemistry at α, β positions. The availability of the substrates, simplicity in experimental procedure and above all, formation of a wide range of products with significant potential applications make this cyclisation cascade synthetically significant.

2.6.4 Decalin and Isoindole Cycloadducts

A cascade route entailing 4π electrocyclic ring-opening combined with Diels–Alder is an attractive approach to establish carbocyclic compounds. Maulide and co-workers have found that a tethered olefin containing *trans*-cyclobutene **250** is amenable to follow a tandem sequence of 4π ring-opening–intramolecular [4+2] cycloaddition and offers decalin cycloadduct **252** as a single diastereomer *via* a triene intermediate **251** (Scheme 36).[14]



Scheme 36 Stereoselective synthesis of cycloadducts **252** and **255** using a tandem conrotatory 4π electrocyclic ring opening–[4+2] cycloaddition sequence.[14]

The protocol works even better for intermolecular Diels–Alder as highlighted for the formation of cycloadduct **255** by the reaction of

trans-cyclobutene **253** with a well-known dienophile, *N*-phenylmaleimide (**254**, scheme 36).[14] The high stereoselectivity of this transformation is due to an absolute control of toruoselectivity during the formation of conjugated dienes as a result of conrotatory 4π electrocyclic ring-opening. Notably, multiple adjacent stereocentres are created in the products by two stereogenic centres present in the starting *trans*-cyclobutenes.

3 Challenges and prospects

Scientific community has expedited tremendous efforts in the domain of 4π electrocyclisation over the last few decades and in recent times, its tentacles are reaching into domino reactions and it has received increasing interest. Despite of current galvanisation in this area of research and documentation of numerous synthetic applications, there are significant concealed aspects to be explored that pose a great challenge to the scientific community. Various cascade reactions of 4π electrocyclisation along with rearrangements and conventional transformations have been eloquently reported however, there is a potential to trigger untouched areas for 4π electrocyclisation tandem reactions, such as induction of cross metathesis, incorporation of olefination strategies, interrupting cyclopentenyl cation in 4π-electron-5-atom systems by nucleophiles that have readily diversified functional groups for further manipulations in a cascade, exploring the possibility of incorporating heteroatoms including halogens, improvement in the control of absolute stereochemistry by controlling the absolute sense of torquoselectivity, mechanistic investigations to get further insight into the reaction intermediates and development of chiral reagents and mild catalysts including phase-transfer for efficient enantioselective and sub-stoichiometric versions of electrocyclisation. As the associated challenges and limitations in this area are addressed, synthetic utility of domino reactions in 4π electrocyclisation will further enhance. These are conspicuous strategies with huge potential and will continue an irresistible allure of fascinating domino combinations and applications towards bioactive natural products and compounds of synthetic interests.

4 Conclusions

This review focuses on the recent most instructive and fascinating tandem reactions in which 4π electrocyclisation is one of the significant transformations. This regio- and stereoselective approach is an effective means of preparing a variety of richly functionalised carbocycles as well as heterocyclic compounds, which are prevalent in medicinal chemistry and natural product synthesis. Synthetic utility of these processes have been highlighted by accomplishing the synthesis of numerous biologically active natural products with profound structural complexity. Furthermore, it is anticipated that the insight provided in this account will be beneficial to elicit further research in this domain.

5 Abbreviations

Ac	Acetyl
Ar	aromatic
atm	atmospheric pressure
Bn	benzyl
Bu	butyl
Cy	cyclohexyl
DABCO	1,4-Diazabicyclo[2.2.2]octane
DCC	*N,N'*-dicyclohexylcarbodiimide
DCE	dichloroethene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DFT	density functional theory
DIBAL-H	diisobutylaluminium hydride
DMAP	4-(dimethylamino)pyridine
DMDO	Dimethyldioxirane
DMF	*N,N'*-dimethylformamide
dr	diastereomeric ratio
ee	enantiomeric excess
EPR	electron paramagnetic resonance
eq.	equivalent
esp	thieno[2,3-B]pyridine-2-carboxamidine
Et	ethyl
HMDS	hexamethyldisilazane
h	hour
LDA	lithium diisopropylamide
Ln	ligand
m-CPBA	3-chloroperoxybenzoic acid
Me	methyl
min	minutes
NMO	*N*-methylmorpholine-*N*-oxide
NOE	Nuclear Overhauser enhancements
Ns	nosyl or *p*-nitrobenzenesulfonyl
Nu	nucleophile
Ph	phenyl
PMB	*p*-methoxybenzyl
PMP	*p*-methoxyphenyl
Pr	propyl
rt	room temperature
TBS	*tert*-butyldimethylsilyl
Tce	trichloroethyl
Tf	triflyl or trifluoromethanesulfonyl
TFA	triflouroacetic acid
TFAA	triflouroacetic anhydride
THF	tetrahydrofuran
TMP	2,4,6-trimethoxylphenyl
TMS	trimethylsilyl
Troc	2,2,2-trichlorethyl chloroformate
Ts	tosyl or *p*-toluenesulfonyl

Acknowledgements

The author gratefully acknowledges the invaluable guidance and continuous encouragement offered by his mentors, Richard C. D. Brown (University of Southampton, UK) and Iain Coldham (University of Sheffield, UK). Also, thanks to the King Faisal University, Saudi Arabia for the support.

References

1 (*a*) M. A. Tius, *Stereoselective Synthesis of Drugs and Natural Products*, ed. V. Andrushko and N. Andrushko, 2013, **1**, 521; (*b*)

E. L. Myers and D. Trauner, *Comprehensive Chirality*, ed. E. M. Carreira and H, Yamamoto, 2012, **2**, 563; (*c*) S. Thompson, A. G. Coyne, P. C. Knipe and M. D. Smith, *Chem. Soc. Rev.*, 2011, **40**, 4217; (*d*) B. Gasper and D. Trauner, *Science of Synthesis, Stereoselective Synthesis*, ed. G. J. De Vries, G. A. Molander and P. A. Evans, 2011, **3**, 383; (*e*) C. M. Beaudry, J. P. Malerich and D. Trauner, *Chem. Rev.*, 2005, **105**, 4757; (*f*) J. C. Namyslo and D. E. Kaufmann, *Chem. Rev.*, 2003, **103**, 1485; (*g*) T. Durst and L. Breau, In *Comprehensive Organic Synthesis*, ed. B. M. Trost, I. Fleming and L. A. Paquette, Pergamon, Oxford, 1991, **5**, 665; (*h*) E. N. Marwell, *Thermal Electrocyclic Reactions*, Academic Press, New York, 1980, Chapter 5, 124.

2 (*a*) I. Fleming, *Molecular Orbitals and Organic Chemical Reactions*, John Wiley & Sons, 2011; (*b*) R. Hoffmann, *Angew. Chem.*, 1982, **94**, 725; *Angew. Chem. Int. Ed. Engl.*, 1982, **21**, 711; (*c*) R. B. Woodward and R. Hoffmann, *The Conservation of Orbital Symmetry*, Verlag Chemie: Weinheim; 1970. (*d*) R. B. Woodward and R. Hoffmann, *Angew. Chem.*, 1969, **81**, 797; *Angew. Chem. Int. Ed. Engl.*, 1969, **8**, 781; (*e*) R. B. Woodward and R. Hoffmann, *J. Am. Chem. Soc.*, 1965, **87**, 395.

3 P. N. Carlsen, T. J. Mann, A. H. Hoyeyda and A. J. Frontier, *Angew. Chem. Int. Ed.*, 2014, **53**, 9334.

4 X. Yan and X. Hu, *J. Org. Chem.*, 2014, **79**, 5282 and refs therein.

5 P. Magnus, W. A. Freund, E. J. Moorhead and T. Rainey, *J. Am. Chem. Soc.*, 2012, **134**, 6140.

6 (*a*) J. A. Malona, K. Cariou, W. T. Spencer III and A. J. Frontier, *J. Org. Chem.*, 2012, **77**, 1891 and refs therein; (*b*) J. A. Malona, K. Cariou and A. J. Frontier, *J. Am. Chem. Soc.*, 2009, **131**, 7560.

7 (*a*) D. Knueppel and S. F. Martin, *Tetrahedron*, 2011, **67**, 9765; (*b*) D. Knueppel and S. F. Martin, *Angew. Chem. Int. Ed.*, 2009, **48**, 2569.

8 W.-D. Z. Li, W.-G. Duo and C.-H. Zhuang, *Org. Lett.*, 2011, **13**, 3538 and refs therein.

9 A. Y. Bitar and A. J. Frontier, *Org. Lett.*, 2009, **11**, 49.

10 S. Gao, Q. Wang and C. Chen, *J. Am. Chem. Soc.*, 2009, **131**, 1410.

11 W. He, J. Huang, X. Sun and A. J. Frontier, *J. Am. Chem. Soc.*, 2008, **130**, 300.

12 S. P. Waters, Y. Tian, Y. Li and S. J. Danishefsky, *J. Am. Chem. Soc.*, 2005, **127**, 13514.

13 V. M. Dembitsky, *J. Nat. Med.*, 2008, **62**, 1.

14 C. Souris, M. Luparia, F. Frébault, D. Audisio, C. Farés, R. Goddard and N. Maulide, *Chem. Eur. J.*, 2013, 6566.

15 C. M. Reisinger, P. Rivera-Fuentes, S. Lampart, W. B. Schweizer and F. Diederich, *Chem. Eur. J.*, 2011, 12906.

16 X. Xin, D. Wang, F. Wu, C. Wang, H. Wang, X. Li and B. Wan, *Org. Lett.*, 2013, **15**, 4512.

17 (*a*) H. Staudinger, *Justus Liebigs Ann. Chem.*, 1907, **356**, 51; (*b*) L. Jiao, Y. Liang and J. Xu, *J, Am. Chem. Soc.*, 2006, **128,** 6060; (*c*) F. P. Cossío, A, Arrieta and M. A. Sierra, *Acc. Chem. Res.*, 2008, **41**, 925.

18 Nazarov cyclization reviews: (*a*) M. A. Tius, *Chem. Soc. Rev.*, 2014, **43**, 2979; (*b*) F. G. West, O. Scadeng, Y.-K. Wu, R. J. Fradette and S. Joy, In *Comprehensive Organic Synthesis*, ed. G. A. Molander and P. Knochel, Elsevier, Oxford, 2014, **5**, 827; (*c*) W. T. Spenser III, T. Vaidya and A. J. Frontier, *Eur. J. Org. Chem.*, 2013, 3621; (*d*) N. Shimada, C. Stewart and M. A. Tius, *Tetrahedron*, 2011, **67**, 5851; (*e*) T. Vaidya, R. Eisenberg and A. J. Frontier, *ChemCatChem*, 2011, **3**, 1531; (*f*) M. J. Fuchter, *Name Reactions for Carbocyclic Ring formations*, ed. J. J. Li and E. J. Corey, Wiley, 2010, 122; (*g*) T. N. Grant, C. J. Rieder and F. G. West, *Chem. Commun.*, 2009, **105**, 5676; (*h*) W. Nakanishi and F. G. West, *Curr. Opin. Drug Discovery Dev.*, 2009, **12**, 732; (*i*) H. Pellissier, *Tetrahedron*, 2005, **61**, 6479; (*j*) A. J. Frontier and C. Collison, *Tetrahedron*, 2005, **61**, 7577; (*k*) M. A. Tius, *Eur. J. Org. Chem.*, 2005, 2193; (*l*) M. Harmata, *Chemtracts*, 2004, **17**, 416; (*m*) K. L. Habermas, S. E. Denmark and T. K. Jones, *Org. React.*, ed. L. A. Paquette, John Wiley & Sons, 2004, **45**, 1–158; (*n*) M. A. Tius, *Acc. Chem. Res.*, 2003, **36**, 284; (*o*) S. E. Denmark, In *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon, New York, 1991, Chapter, 5.6.3, 751; (*p*) K. L. Habermas, C. Santelli-Rouvier and M. Santelli, *Synthesis*, 1983, 429.

19 (*a*) S. Raja, M. Nakajima and M. Rueping, *Angew. Chem. In. Ed.*, 2015, **54**, 2762 and refs therein; (*b*) J. Davies and D. Leonori, *Chem. Commun.*, 2014, **50**, 15171 and refs therein.

20 T. D. R. Morgan, L. M. LeBlanc, G. H. Ardagh, R. J. Boyd and D. J. Burnell, *J. Org. Chem.*, 2015, **80**, 1042.

21 C. Piutti and F. Quartieri, *Molecules*, 2013, **18**, 12290 and refs therein.

22 G. K. Veits, D. R. Wenz and J. R. de Alaniz, *Angew. Chem. In. Ed.*, 2010, **49**, 9484.

23 (*a*) B.-L. Yin, Y.-L. Wu and J.-Q. Lai, *Eur. J. Org. Chem.*, 2009, 2695; (*b*) M. D'Auria, *Heterocycles*, 2000, **52**, 185.

24 M. J. Di Grandi, *Org. Biomol. Chem.*, 2014, **12**, 5331 and refs therein.

25 J. S. Alford, J. E. Spangler and H. M. L. Davies, *J. Am. Chem. Soc.*, 2013, **135**, 11712.

26 S. M. Bachrach, *Computational Organic Chemistry*, 2nd edition, Wiley, 2014.

27 (*a*) M. Murakami and T. Matsuda, *Comprehensive Organic Synthesis II*, ed. P. Knochel and G. A. Molander, 2014, **5**, 732 and refs therein; (*b*) W. R. Dolbier Jr, H. Koroniak, K. N. Houk and C. Sheu, *Acc. Chem. Res.*, 1996, **29**, 471.

28 (*a*) L. F. Tietze, *Domino Reactions: Concepts for Efficient Organic Synthesis*, John Wiley & Sons, 2014; (*b*) L. J. Patalog and D. B. Wertz, *Domino Reactions*, ed. L. F. Tietze, 2014, 183; (*c*) H. Pellissier, *Asymmetric Domino Reactions*, RSC Catalysis Series, The Royal Society of Chemistry, 2013.

29 Y. Jiang and C.-M. Park, *Chem. Sci.*, 2014, **5**, 2347.

30 H. Zheng, X. Xie, J. Yang, C. Zhao, P. Jing, B. Fang and X. She, *Org. Biomol. Chem.*, 2011, **9**, 7755.

31 I. Nakamura, D. Zhang and M. Terada, *Tet. Lett.*, 2011, **52**, 6470.

32 D. Fisher, L. I. Palmer, J. E. Cook, J. E. Davis and J. R. de Alaniz, *Tetrahedron*, 2014, **70**, 4105.

33 L. I. Palmer and J. R. de Alaniz, *Org. Lett.*, 2013, **15**, 476.

34 L. I. Palmer and J. R. de Alaniz, *Angew. Chem. Int. Ed.*, 2011, **50**, 7167.
35 D. R. Wenz and J. R. de Alaniz, *Org. Lett.*, 2013, **15**, 3250.
36 D. Yu, V. T. Thai, L. I. Palmer, G. K. Veits, J. E. Cook, J. R. de Alaniz and J. E. Hein, *J. Org. Chem.*, 2013, **78**, 12784.
37 D. Lebœuf, E. Schulz and V. Gandon, *Org. Lett.*, 2014, **16**, 6464.
38 F. Li, C. Ding, M. Wang, Q. Yao and A. Zhang, *J. Org. Chem.*, 2011, **76**, 2820.
39 B. V. S. Reddy, Y. V. Reddy, P. S. Lakshumma, G. Narasimhulu, J. Yadav, B. Sridhar, P. P. Reddy and A. C. Kunwar, *RSC Adv.*, 2012, **2**, 10661.
40 Y. Wang, W. Liao, G. Huang, Y. Xia and Z.-X. Yu, *J. Org. Chem.*, 2014, **79**, 5684 and refs therein.
41 C. Kong and T. G. Driver, *Org. Lett.*, 2015, **17**, 802.
42 C. Kong, N. Su, F. Zhou, N. Jana and T. G. Driver, *Tetrahedron*, 2015, **56**, 3262.
43 C. Kong, N. Jana and T. G. Driver, *Org. Lett.*, 2013, **15**, 824.
44 D. Lebœuf, V. Gandon, J. Ciesielski and A. J. Frontier, *J. Am. Chem. Soc.*, 2012, **134**, 6296.
45 D. Lebœuf, C. M. Wright and A. J. Frontier, *Chem. Eur. J.*, 2013, 4835 and refs therein.
46 D. Lebœuf, J. Huang, V. Gandon and A. J. Frontier, *Angew. Chem. In. Ed.*, 2011, **50**, 10981.
47 J. Huang, D. Lebœuf, and A. J. Frontier, *J. Am. Chem. Soc.*, 2011, **133**, 6307.
48 D. Lebœuf, E. Theiste, V. Gandon, S. L. Daifuku, M. L. Neidig and A. J. Frontier, *Chem. Eur. J.*, 2013, 4842.
49 X.-N. Wang, E. H. Krenske, R. C. Johnston, K. N. Houk and R. P. Hsung, *J. Am. Chem. Soc.*, 2015, **137**, 5596.
50 G. Rosocha and R. A. Batey, *Tetrahedron*, 2013, **69**, 8758–8768.
51 S.A. Bonderoff, T. N. Grant, F. G. West and M. Tremblay, *Org. Lett.*, 2013, **15**, 2888.
52 K. Sugimoto, R. Hayashi, H. Nemoto, N. Toyooka and Y. Matsuya, *Org. Lett.*, 2012, **14**, 3510.
53 Y. Wang, Y. Chi, W.-X Zhang and Z. Xi, *J. Am. Chem. Soc.*, 2012, **134**, 2926.
54 J. L. Brooks, Y.-W. Huang and A. J. Frontier, *Org. Synth.*, 2014, **91**, 93.
55 J. L. Brooks and A. J. Frontier, *J. Am. Chem. Soc.*, 2012, **134**, 16551.
56 J. L. Brooks, P. A. Caruana and A. J. Frontier, *J. Am. Chem. Soc.*, 2011, **133**, 12454.
57 W. T. Spencer III, M. D. Levin and A. J. Frontier, *Org. Lett.*, 2011, **13**, 414.
58 M.-J. Zhong, X.-C. Wang, H.-T. Zhu, J. Hu, L. Liu, X.-Y. Liu and Y.-M. Liang, *J. Org. Chem.*, 2012, **77**, 10955.
59 Y.-K. Wu and F. G. West, *Org. Lett.*, 2014, **16**, 2534.
60 Y.-K. Wu, R. McDonald and F. G. West, *Org. Lett.*, 2011, **13**, 3584.
61 M. Wang, F. Han, H. Yuan and Q. Liu, *Chem. Commun.*, 2010, **46**, 2247.
62 M. J. Riveira and M. P. Mischne, *J. Org. Chem.*, 2014, **79**, 8244.
63 C. Theunissen, B. Métayer, N. Henry, G. Compain, J. Marrot, A. Martin-Mingot, S. Thibaudeau and G. Evano, *J. Am. Chem. Soc.*, 2014, **136**, 12528.